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455 *Advances in rabies control*

462 *Poliomyelitis prevention*

469 *Chagas' disease*

471 *Cirrhosis of the liver in France*

473 *Postage of perishable biological material*

474 *Iodine prophylaxis of endemic goitre*

476 *Notes and news*

482 *People and places*

484 *Review of WHO publications*

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ADVANCES IN RABIES CONTROL

In 1958, in 65 out of 108 countries and territories to which WHO addressed a questionnaire about rabies, nearly 500 000 persons received antirabies treatment, mostly after having been bitten; 865 persons died without having received treatment; 82 died during or after treatment; and 49 developed paralytic complications after vaccination. Incomplete though these figures are, they represent a great deal in terms of human suffering and effort. Each of the 500 000 persons vaccinated had a series of, on the average, 14 or 15 painful injections keeping him (and often his family too) for weeks close to the institution where he was getting the injections. Each person, also, was in fear of death, should the treatment fail—a fear prolonged sometimes for months, since the incubation period of the disease may be long. Laboratory workers producing the vaccine had to manipulate dangerous viruses, inoculate them into the nervous systems of the animals whose brains or spinal cords were used as vaccination material, treat these tissues by inactivating agents in special apparatus and test vaccine potency in guinea-pigs, rabbits or mice—for which several weeks of work were often required. Humanity still pays a heavy tribute of suffering to this frightful disease. But whereas before the time of Pasteur it occurred frequently following the bite of a rabid animal, it is now much rarer, thanks to the increasing effectiveness of vaccination methods resulting from collaboration on an international scale; for rabies, if untreated, has such a terrifying outcome that countries and continents early came together to devise methods of combating it.

Since the International Rabies Conference in 1927, as a result of which the Health Organisation of the League of Nations was entrusted with the task of collecting, on the basis of questionnaires to countries with suitable institutes, data on the number of cases of rabies, the results of treatment, and the effectiveness of the various kinds of vaccine, international work on the disease has continued unabated. In the last ten years in particular, there has been considerable progress, WHO aiding by giving assistance to laboratories, organizing surveys, facilitating exchanges of views and material among research workers, bringing experts together, and disseminating through its publications knowledge of methods of producing and testing vaccines. In this way WHO has imparted momentum to research into rabies and to the practical application of the results achieved. The fresh advances are briefly described in this article, the source of which is the replies of 89 countries and territories to the latest questionnaire on the subject sent out by WHO [1] and the recently published fourth report of the WHO Expert Committee on Rabies.[2]

Distribution of rabies in the world and sources of infection

The WHO questionnaire was sent to some 300 laboratories, institutes, health organizations, and veterinary departments in 109 countries and territories. It was very favourably received, and the 222 replies from 89 countries give a general picture of rabies throughout the world. Of the 109 countries consulted, 63 had recorded cases of rabies in 1958, 26 had been free from the disease, and 20 gave no information.

Which rabid animals are most dangerous to man? The rabies virus has been found in a large number of animals, but not all transmit the infection. While one of the animals most liable to transmit infection is the dog, in many countries—particularly those where canine rabies has been brought under control—wild animals are more dangerous in this respect. In Germany, Canada, parts of the USA, and Poland, the fox plays a greater part than the dog in spreading rabies, in the USA the skunk

[1] These replies are analysed in unpublished working document Rabies/Inf.1.

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1960, 201

is an important vector, and, in the continent of America especially, insectivorous bats have begun to assume prominence as vectors—whereas up to 1953 only the vampire bats of South America had been known to be carriers of the disease. In 1953 the rabies virus was isolated for the first time from an insectivorous bat and since then it has been isolated hundreds of times, in 24 of the states of the USA and in one Canadian province, from mainly gregarious but also from solitary bats. Infection in bats is not confined to America—it has been reported in Turkey and Yugoslavia, and has been suspected in one case in Western Germany and in India.

In Asia, jackals, wolves, and foxes are, with dogs, the animals whose bites are most to be feared. A well-known instance [3] is that of the rabid wolf that came down some years ago from the high plateaux of Iran and attacked sleeping villagers, biting them savagely. Among these villagers some escaped death only because of a relatively new form of treatment, in which serum was combined with the vaccine (see below).

Vaccination against rabies

Ever since Pasteur showed the way, virologists have been concerned to protect human beings from the suffering caused by the introduction of rabies virus into the nervous system by the bite of an infected animal—a pathological process unique of its kind. Nevertheless, from 1885—the date when vaccination with dried rabbit spinal cord was first introduced—to 1925, progress was slow and attempts at innovation were for the most part short-lived. Only after that date were new paths opened up with the development of immunological research and improvement in techniques for preparing vaccines and sera and in methods of assessing their activity—all this work being stimulated by international collaboration.

In the past few years progress has been spectacular. A method of effectively vaccinating persons bitten by rabid animals with serum and vaccine has been developed; vaccines have been prepared from chicken and duck embryos, which are almost free from the factor responsible for post-vaccinal allergic encephalitis, and which can be freeze-dried and so kept in a stable form; and a hyperimmune serum, prepared from animals and with antibodies concentrated by special processes, has been tested and adopted. With these advances more effective methods of prophylaxis are now feasible.

Post-exposure treatment with serum and vaccine

As the fourth report of the WHO Expert Committee on Rabies says: " . . . this [combined serum and vaccine treatment] is definitely the best method now available "; it is specially indicated in severe exposures (head and neck bites). Protection against rabies depends on active immunization, achieved by the production of antibodies under the stimulus of the vaccine. But, even if the first of the large number of injections needed is carried out immediately after the bite, several days elapse before antibodies are detectable in the serum. During this period the virus inoculated with the bite of the animal may multiply, particularly if it is inoculated in large quantity, outstripping the defensive measures and thus causing them to fail. With a view to obviating this danger and creating an immediate barrier to the virus, a method of treatment with serum was tested for some years and then adopted, and it now forms a part of standard immunization methods. Serum with a high antibody content (hyperimmune serum) is used; it is prepared usually from horses, donkeys or mules, and is injected along with the first dose of vaccine. By temporarily slowing down or halting the multiplication of the virus, it gives time for active immunity to develop. The dose should be not less than 40 International Units (1 IU = 1 mg) per kg of body weight, followed by a course of not less than 14 daily doses of vaccine when the full treatment is given. Two supplemental doses of vaccine—preferably with a vaccine of other than nervous tissue—should be administered 10 and 20 days after completion of the course of vaccinations. This is an innovation and was introduced

[3] *Chron. Wld Hlth Org.*, 1955, 9, 308

TABLE 1. GUIDE FOR SPECIFIC POST-EXPOSURE TREATMENT

Nature of exposure	Biting animal *		Recommended treatment ** (in addition to local treatment)
	At time of exposure	During observation period of ten days	
I. No lesion; indirect contact	Rabid	—	None
II. Licks :			
(1) unabraded skin	Rabid	—	None
(2) abraded skin, scratches and unabraded or abraded mucosa	(*a*) healthy	Clinical signs of rabies or proven rabid (laboratory)	Start vaccine at first signs of rabies in the biting animal
	(*b*) signs suggestive of rabies	Healthy	Start vaccine immediately; stop treatment if animal is normal on fifth day after exposure
	(*c*) rabid, escaped, killed or unknown	—	Start vaccine immediately
III. Bites:			
(1) mild exposure	(*a*) healthy	Clinical signs of rabies or proven rabid (laboratory)	Start vaccine at first signs of rabies in the biting animal
	(*b*) signs suggestive of rabies	Healthy	Start vaccine immediately; stop treatment if animal is normal on fifth day after exposure
	(*c*) rabid, escaped, killed or unknown	—	Start vaccine immediately
	(*d*) wild (wolf, jackal fox, bat, etc.)	—	Serum immediately, followed by a course of vaccine †
(2) severe exposure (multiple, or face, head, finger or neck bites)	(*a*) healthy	Clinical signs of rabies or proven rabid (laboratory)	Serum immediately; start vaccine † at first sign of rabies in the biting animal
	(*b*) signs suggestive of rabies	Healthy	Serum immediately; followed by vaccine; vaccine may be stopped if animal is normal on fifth day after exposure
	(*c*) rabid, escaped, killed or unknown (*d*) wild (wolf, jackal, fox, bat, etc.)	—	Serum immediately; followed by vaccine †

* This schedule applies equally whether or not the biting animal has been previously vaccinated.

** For the benefit of physicians who will use this guide, a detailed history of exact circumstances of exposure is essential to determine the action to be taken.

The general principles on which the foregoing guide is based are that in mild exposures a course of vaccine following local treatment is sufficient, whereas following severe exposures, and in all cases of unprovoked wild animal bites, antirabies serum together with vaccine should be employed. As with vaccine alone, it is important to start combined serum and vaccine treatment as early as possible after exposure. Serum should be administered in a single dose (not less than 40 International Units per kg of body-weight) at the start of treatment, followed by a course of not less than 14 daily doses of vaccine. In all cases where serum is followed by a full course of vaccine it is suggested that two supplemental doses of vaccine be administered at 10 and 20 days following the completion of the usual vaccine schedule. Where possible, these supplemental doses should be with a vaccine of non-nervous-tissue origin.

Sensitivity to serum should be tested before serum is used.

It is fully recognized that this table is only a guide and in certain situations specific conditions may warrant modifications, e.g., exposure, especially in young children or where a reliable history cannot be obtained, and particularly in areas where rabies is known to be enzootic even though the animal at the time of exposure is considered to be healthy. Such cases may justify treatment immediately in a modified way. Possible modifications would be that, following local treatment of the wound, a single dose of serum or three doses of vaccine at daily intervals, and no further vaccine, be given as long as the animal stays healthy for 10 days following exposure.

Another example of a local situation in which a modified interpretation of these recommendations may be indicated is that of rabies-free areas where frequent exposures to animal bites are encountered. In such localities, adequate laboratory and field experience indicating no infection in the species involved may justify the local health authorities in recommending no specific antirabies treatment.

† Course of vaccine to be followed by supplemental doses of vaccine of non-nervous tissue if possible, 10 and 20 days after the last usual dose.

because experimental work indicated that serum partially inhibits the production of active immunity by the vaccine; the two supplemental doses of vaccine exert a booster effect (see below). Table 1 provides a guide for the treatment of persons exposed to the risk of contracting rabies. It was drawn up by the WHO Expert Committee on Rabies, and replaces the table appearing in the Committee's third report.

To increase the chances of success, this treatment with serum and vaccine should be supplemented by local treatment of the wounds with various antiseptics. Such local treatment has been the subject of numerous studies.[4] Another suggestion is that part of the dose of serum should be injected into the tissues underlying the wound, and Soviet research workers recently advocated the local application of powdered gamma globulin containing antibodies against rabies. This procedure is at present under study.

Immunization before exposure

Particular groups of individuals, such as veterinarians, dog handlers, field naturalists, and laboratory workers, are unusually exposed to the risk of being bitten by rabid animals. To vaccinate them each time they are bitten would be to increase the possibilities of their having severe reactions to the vaccine. Two types of vaccine have accordingly been prepared—the duck-embryo and the HEP chicken-embryo vaccines—for the prophylactic vaccination of these groups; both are almost devoid of encephalitogenic properties. The immunization schedule suggested is three intradermal doses 5 to 7 days apart, followed by a booster dose administered one or more (preferably 2-6) months after the last dose of vaccine. However, not all vaccinated individuals give an antibody response, and booster doses should be repeated till antibody is detectable. A single injection of potent antirabies vaccine given even a long time after antirabies treatment results in a prompt and significant antibody rise; consequently, a single booster dose is sufficient for a person who has had the treatment and has shown an antibody response, if he is mildly exposed. If, however, the exposure is severe it would be preferable, until further information becomes available, for him to undergo the full treatment with serum and vaccine.

Vaccines and their production

Since the pioneer days of vaccination—the age of Pasteur, when vaccines were more or less virulent according to the extent that they had been dried, the preparation of vaccines has taken great steps forward. Table 2 shows the vaccines now available for immunization of man and animals.

TABLE 2. VACCINES AVAILABLE FOR IMMUNIZATION OF MAN AND ANIMALS

Vaccine	Strain of virus	Tissue used for preparation of vaccine	For use in:
Live virus:			
LEP *	Flury, 40-60 egg passage	Chicken embryo	Dog
K *	Kelev	Chicken embryo	Dog and cattle
HEP *	Flury, above 180th egg passage	Chicken embryo	Cattle, cat, dog and man
Nervous tissue *, **	Fixed	Central nervous system	Man, dog, cattle and other animals
Inactivated:			
Duck *	Fixed virus	Duck embryo	Man
Nervous tissue *, **	Fixed virus	Central nervous system	Man, dog, cattle, and other animals

* Available in freeze-dried form
** Available in liquid form

There are on the one hand *live virus vaccines*—fixed viruses (*a*) propagated on nervous tissue from inoculated animals and used as vaccines in greater or lesser dilutions (from 1:8000 to 1:20 000) or (*b*) propagated on chicken embryo. The latter, if of the Flury strain, have either undergone relatively few

[4] See *Bull. Wld Hlth Org.*, 1954, **10**, 805; 1957, **17**, 963.

(40-60) passages through chicken embryo (LEP), or have undergone more than 180 passages (HEP), which decreases their virulence still more and makes them suitable for use in man and animals.

On the other hand, there are *inactivated vaccines*, treated with phenol or ultra-violet rays, and prepared either from animal nervous tissue or on duck embryo. The strain of fixed virus used at the Institut Pasteur, Paris, is—it is of interest to note—in the direct line of the one Pasteur himself used for the first attempts at vaccination in 1885. This strain has been kept going in rabbits and has undergone more than 2000 passages since the culture was originally made.

Not all strains of virus can be used for the preparation of vaccines. The WHO Expert Committee on Rabies recommended at its last session that for the production of any vaccine a particular strain of virus should be used that has given satisfactory results in the laboratory and in the field. Such a strain is obtainable from WHO on request.

Of the 137 institutes approached by questionnaire, 94 replied that they were producing vaccine. At least 66 of them produce vaccine for use in human beings, 52 for use in animals, and 30 for both. At the head of the list comes the Semple type vaccine, followed by the Fermi type. Ultra-violet ray irradiated vaccine is produced by only four institutes (in Chile, Japan, India, and the USA), because of the special equipment needed. Avianized vaccines are produced especially for use in animals. A few institutes do however produce HEP and duck embryo vaccines for use in man, these vaccines having the advantage of being practically free of encephalitogenic properties. Sheep are the animals mainly employed for the preparation of vaccine in nervous tissue, but rabbits are also in common use. Other animals employed for the preparation of human vaccines are the mouse, monkey and guinea-pig; and for animal vaccines the buffalo, calf, dog, horse, donkey and mouse.

Of the 94 institutes producing vaccine, 78 use a potency test, and 8 do not; 8 did not reply on this point.

The *international reference vaccine* was found useful by 29 laboratories. Since 1957 this vaccine has been placed by WHO at the disposal of laboratories wishing to check the potency of their own products. It is a dried ultra-violet ray inactivated vaccine, the first batch of which (155D) was rapidly exhausted. It has recently been replaced by a second batch (164), prepared by the US National institutes of Health (NIH).

The WHO Expert Committee urged in its recent report that each national laboratory prepare its own stock of reference vaccine, which, after comparison with the international reference vaccine, could be used to supply other laboratories in the country. This is made more practicable by the recent development in the USSR of a method of freeze-drying phenolized vaccine. Ideally, the reference vaccine prepared by each country should be used in the potency testing of every batch of vaccine produced by individual laboratories by the NIH potency test technique.

As for the schedule of vaccination in human beings, most institutes give 7-14 vaccinations, the total amount of nervous tissue for the complete course of treatment varying between 1 and 4 g (60 institutes) and being over 6 g with only 2 institutes.

Antirabies serum

Serum with a high antibody concentration—the so-called hyperimmune serum—is prepared in 28 of the institutes that answered the questionnaire, and all used equines for the purpose. While 8 of the institutes employ the serum for experimental purposes only, 18 use it for treatment in conjunction with vaccine. In antirabies prevention in the USSR gamma globulin is used in a dose of 0.25 ml per kg body weight.

The opinion of the institutes producing vaccine was that treatment with serum should be used mainly for severe cases, especially when there have been bites on the head, neck and face, and that it should be given as soon as possible after exposure. Twelve of these institutes assess the potency of their serum by the international standard serum. In its recent report, the WHO Expert Committee reviewed the technique of potency testing and pointed

out that the International Standard for Antirabies Serum is in the custody of the Statens Seruminstitut, Copenhagen, which will make it available on request.

Drawbacks to treatment and ways of dealing with them

Reactions to antirabies horse serum, even though the serum is purified and concentrated, occur to approximately the same degree as with other animal sera (in roughly 20% of cases). Possible allergic reactions should therefore be avoided by taking a careful history of any previous allergy and by routine sensitivity testing—and, if there is sensitivity, by desensitization. The incidence of serum sickness can be reduced by administration of antihistamines.

As for neuroparalytic complications after treatment with nervous-tissue vaccine, these vary in frequency from country to country, for unknown reasons. The type of population involved, the physiological state of the individual, the species of animal used for the production of the vaccines, the method of inactivation, or the dosage schedule may play a part. These accidents are sufficiently common in some parts of the world for research to be carried out in an effort to put an end to them. While avian vaccines may take the place of nervous-tissue vaccines when symptoms give rise to the fear that neurological complications may occur, they should not be given to persons known to be sensitive to egg protein without proper precautions.

Since the beginning of combined serum-vaccine treatment it has been observed that the serum inoculated with the first dose of vaccine inhibits to a greater or lesser extent the production of antibodies stimulated by the vaccine. This inhibition is particularly noticeable in short courses of treatment, when the number of injections of vaccine is less than 14; and the serum may even interfere with the ability of the subject to respond to a booster dose of vaccine given 30, 60 or 120 days after the first course—a response that usually appears within 8 days as a rise in the antibody level. The schedule of treatment was drawn up so as to reduce the inhibiting effect of the serum to the greatest possible degree.

Fluorescent antibody test

The classic diagnostic tecnniques (examination for Negri bodies, isolation of the virus, and the sero-neutralization test) have recently been supplemented by new methods, in particular the fluorescent antibody test. This test, to quote the Committee's report, " is based upon the microscopic examination of tissue specimens for specific fluorescent staining when the tissue is placed in contact with antirabies serum which has been 'tagged' (or 'labelled') by the addition of a fluorescent dye. This fluorescence is visual evidence of specific antigen-antibody reaction . . . The investigations of this diagnostic method have revealed that this test, when properly executed, can establish a highly specific diagnosis on test specimens within a few hours, and that there is a high degree of correlation between the fluorescent antibody and the mouse inoculation test."

The Committee wished " to encourage rabies diagnostic laboratories to develop proficiency in carrying out this test in order that further comparative studies can be done with this and other diagnostic tests ". It pointed out, however, " that exacting standards of performance, equipment and reagents are necessary and these are related to adequate training and proficiency of the diagnostician as well as to the quality of reagents and equipment employed ".

Control of reservoirs and vectors

To improve the situation and in the long run to achieve the ultimate aim of eliminating rabies, action must be taken against the animal reservoirs or vectors of infection by destruction or vaccination. Mention has already been made of the large number of species that can carry the infection. The WHO Expert Committee devoted special attention to dogs, on the ground that vaccination of dogs is one of the strongest weapons against rabies in countries where there are infected areas. Full details on the immunization of dogs, and also of cats and cattle, will be found in the report. Stray dogs that miss being vaccinated and are potential sources of infection should preferably be destroyed. As a

result of measures of this kind—vaccination and destruction—there was a striking drop in the incidence of rabies in Israel and Malaya.[5] In reply to one of the questions in the questionnaire, 9 countries where rabies occurs said that they had no restrictive legislation, while 36 countries in which rabies is endemic and 21 that are free from rabies said that they had issued regulations to prevent the introduction of rabies-infected animals.

But the most serious unknown factors are wild animals, the least controllable sources of rabies virus. The role of the fox has been mentioned. In Canada, it was found in 1947 that foxes and wolves had become important reservoirs of the disease. Rabid animals lose their wildness, enter camps, mix with sledge animals and accompany the teams (the " mad " foxes of the trappers). Intensive hunting of the fox and the wolf for their skins during the first quarter of the century undoubtedly reduced their numbers; but with the fall in the value of their skins they began to increase again, and, moving southwards, perhaps in pursuit of the small animals on which they prey, they have occupied areas formerly free from rabies.[6] The fact that rabies is detectable in foxes by visible signs of involvement of the nervous system enables the animals to be tracked down—they are not believed to be " asymptomatic carriers ". But it has been shown that the disease affects the animal for a fairly long period, during which its saliva is infectious—and this prolongs the danger.

[5] *Chron. Wld Hlth Org.*, 1954, **8**, 263
[6] *Bull. Wld Hlth Org.*, 1954, **10**, 767

Trapping, poisoned baits (e.g., thallium sulfate for mongooses and strychnine-treated eggs for skunks), and gassing of dens are among the most effective procedures in use for control, with the aim of reducing the population level to a threshold that will no longer be able to support an epizootic of rabies.

The role of " silent carriers " played by bats has been mentioned. It is impossible at present to recommend defence measures against these animals, unless perhaps to use naphthalene flakes or fumigant gases to rid human dwellings of them, and then take steps to prevent their return.

The WHO Expert Committee warned against picking up or handling sick bats or bats behaving strangely. Persons bitten by bats should be given antirabies treatment.

Future research

Among the subjects that deserve further study are the local treatment of bites; the best method of injecting non-nervous-tissue vaccine (intradermally or subcutaneously); the stability of freeze-dried phenolized vaccine; improvement in the methods of rapid diagnosis; the development of highly antigenic non-nervous-tissue vaccines; the production of hyperimmune serum of human origin; the cultivation of rabies virus on tissue culture; and the possibility of using tissue culture for preparing a non-nervous-tissue vaccine for use in human beings. Finally, there are the problems of ecology, the pathogenesis of rabies in animals, and the detection of unknown reservoirs.

POLIOMYELITIS PREVENTION

Only six years ago, a WHO Expert Committee on Poliomyelitis [1] stated that "vaccination procedures against poliomyelitis are still in an experimental stage, and that 'poliomyelitis vaccines' of unquestionable value are not yet available for general use". In that short space of time, extraordinary progress has been made in the development of active immunization procedures and vaccination against poliomyelitis is already being practised on a very extensive scale. Not only have inactivated vaccines been used for this purpose but, within the last three years, intensive studies have been made of live attenuated poliovirus vaccines and in some countries they have been used successfully for mass immunization programmes. Experience with live poliovirus vaccine from 1957 to 1959 and some of the problems raised by its use were reviewed recently in the *WHO Chronicle*,[2] following an international conference on the subject convened jointly by WHO and the Pan American Health Organization in June 1959. A second conference was held in June 1960 and the information collected placed before the Expert Committee on Poliomyelitis [3] which met immediately afterwards. In its third report [4] the Committee evaluates this material as well as the most recent experience with inactivated vaccines, and formulates a number of recommendations for future policy and research.

Inactivated vaccines

In most countries where inactivated vaccines have been widely used, the protection obtained has been of the order expected on the basis of field trials. In the USA, more than 300 million doses of vaccine have been used for vaccination programmes within the country. During 1959, it was estimated that the effectiveness ratios in triply vaccinated persons were over 90% in the age-group 0-14 and 82% in the age-group 15-39. For persons vaccinated 4 times, the ratios were 96% and 86% respectively. The data on which these estimates were based were derived mainly from the case reports submitted to the Poliomyelitis Surveillance Unit, from the Census Bureau random sample survey, and from an intensive study of a local epidemic in Des Moines, Iowa. In the latter epidemic, cases were found to be concentrated in the central areas of the city, in contrast to experience before immunization. The highest rates were found in the poorly vaccinated lower socio-economic group of the population, a finding confirmed in other local epidemics.

During an outbreak of poliomyelitis in Winnipeg, Canada, in 1958, the attack rate per 100 000 in the age-group 5-9 was found to be 9 times as high among unvaccinated as among vaccinated children; in the age-group 10-14 it was 4.5 times as high. In Canada as a whole, the reduction in cases of poliomyelitis attributable to vaccination during 1958 was estimated to be around 98%, while during 1959 the over-all effectiveness rate was estimated to be 96%.

In England and Wales, where 6 000 000 children had received 2 or more doses of inactivated vaccine by the end of 1958, the attack rates were 4.3 per 100 000 in vaccinated children and 21.4 per 100 000 in unvaccinated children. The corresponding rates for paralytic cases were 2.4 per 100 000 and 15.1 per 100 000. The fatality rate was over 10 times as high in the unvaccinated as in the vaccinated children.

Somewhat similar figures have been reported from Australia, the Union of South

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1954, **81**, 29

[2] *WHO Chronicle*, 1959, **13**, 402; 1960, **14**, 137, 142

[3] Members of the Committee: Sir Macfarlane Burnet, Australia; Professor S. Gard, Sweden; Dr J. H. S. Gear, Union of South Africa; Dr R. Murray, USA (Rapporteur); Professor J. R. Paul, USA; Dr V. Skovranek, Czechoslovakia; Professor C. H. Stuart-Harris, United Kingdom (Chairman); Professor V. M. Zhdanov, USSR (Vice-Chairman). Secretariat: Dr A. N. Bica, PASB/WHO; Dr R. Dulbecco, USA (Consultant); Dr A. M.-M. Payne, WHO (Secretary); Dr M. N. da Silva, PASB/WHO.

[4] *Wld Hlth Org. techn. Rep. Ser.*, 1960, **203**

Africa and a few other countries, but there have also been some less favourable experiences. In the islands of Rodriguez and Mauritius, intensive vaccination failed to stop an epidemic of poliomyelitis although there was a marked difference in rates between vaccinated and unvaccinated persons. In the Moscow region of the USSR, little change was noticed in the incidence of poliomyelitis between 1955 and 1959, although nearly all children under the age of 14 years had been vaccinated. For the USSR as a whole, there was a decrease from about 20 000 cases per annum in the period 1955-1957 to about 12 000 in 1958, by which time a total of 15 million persons had been vaccinated. This decrease was considered too small and a programme of live virus administration initiated, as described below. Unsatisfactory results have also been reported from Czechoslovakia and from Hungary, where an epidemic with an attack rate of 24 per 100 000 broke out in 1959 in spite of a vaccination programme covering about 70% of the age-group 6 months to 19 years.

Differences in the mode of administration and variations in potency may be partly responsible for these discrepant findings, as shown by experience in Sweden. Using Swedish vaccines, conversion rates between 65% and 100% were obtained, whereas with imported vaccines the conversion rates were 20-35%. The ratio of observed to expected cases was 0.28 for imported vaccines, but only 0.035 for domestic vaccines.

No serious production or testing problems have been encountered during the last three years. Methods of inactivation have remained virtually unchanged, and the various national requirements and the recommendations issued by WHO have been demonstrated to assure a safe vaccine which has been satisfactory in use. In the light of this experience there seems to be less cause for concern regarding the strain composition of inactivated vaccines, and some countries have used alternative strains. The choice of vaccine strain depends mainly on its suitability to the manufacturing process and its ability to produce a vaccine of acceptable antigenicity. Unfortunately, there is as yet no international agreement regarding acceptable antigenicity levels and the best methods of antigenicity testing. Under the auspices of WHO, a collaborative international assay is at present being conducted, using a number of different vaccines and comparing the various antigenicity tests in use. It is hoped that once a satisfactory antigenicity test has been selected it will also enable information to be obtained on the stability of poliomyelitis vaccines under various conditions of storage.

A number of polyvalent vaccines containing poliomyelitis antigen have recently been given a trial in several countries. Some special manufacturing and testing problems have been encountered, such as the undesirable effect on the spinal cord of monkeys of the adjuvants used; a revised potency testing procedure is needed. Some combinations appeared to show an enhanced potency when injected into animals, although no potentiating effect could be demonstrated in children. It has therefore been necessary to perform the safety and potency tests on the poliomyelitis antigen alone, as well as on the final product. The use of multiple antigens would enable at least some of the doses of poliomyelitis vaccine needed for immunization to be administered along with the usual immunizations of early childhood, but experience is still too limited for their value to be properly assessed.

Live poliovirus vaccination

In addition to the large-scale trials already described in the *WHO Chronicle*,[5] mass immunization with live poliovirus vaccines has been practised in several other countries of eastern Europe, Asia, southern Africa and Latin America. A nation-wide immunization programme with monovalent and with trivalent Lederle vaccines was started in 1959 in Costa Rica; by April 1960 more than 120 000 children under 11 years of age had received all three doses of monovalent vaccine and nearly 150 000 had received at least one dose of trivalent vaccine. In addition some 2000 newborn children received a bivalent vaccine

[5] *WHO Chronicle*, 1960, **14**, 137, 142

(types 2 and 3) during the first 48 hours of life, followed by a monovalent vaccine (type 1) at about 1 month of age. Conversion rates were good for types 1 and 3 in all these studies, but rather low for type 2. In the metropolitan area of San José, the attack rate in 1960 was 168 per 100 000 among unvaccinated children and 14 per 100 000 among vaccinated children. Very similar results were obtained in the department of Managua, Nicaragua, where approximately 50 000 children between the ages of 2 months and 10 years were vaccinated in the period July 1958 to May 1959. In Uruguay, about 325 000 persons of all ages in the city of Montevideo were given monovalent Lederle vaccines, types 2, 3 and 1 in that order, beginning in May 1958, but an outbreak of poliomyelitis developed in October 1958 before type 1 vaccine had been administered. Among the population of Montevideo there were 87 paralytic cases, mostly due to type 1 virus.

Studies with Sabin strains have been made in Mexico. Following favourable results of preliminary trials, large-scale field programmes were initiated in February 1959 in Mexico City, Monterrey, Guadalajara, and Puebla. Monovalent vaccines were used, administered at intervals of 3-4 weeks. Approximately 150 000 children under the age of 5 were vaccinated, representing 17-52% of the age-group, depending upon the area. Poliomyelitis due to type 1 virus was already present in all four cities and after the start of the programme 660 cases occurred in unvaccinated children and 35 among those who had been vaccinated. A programme aiming at more complete coverage was initiated in August 1959 in Toluca, where 80% of the population under 11 years of age—a total of 26 000 children—received a trivalent mixture of the 3 Sabin strains within a period of 4 days. In this way, it was hoped to overcome the phenomenon of interference by enteroviruses. Serological conversion rates 10 weeks after vaccination were 68%, 82% and 43% for types 1, 2 and 3 virus respectively. A second dose administered to 44 children who had failed to respond to one or more types gave conversion rates after another 6 weeks of 96%, 96% and 72% respectively.

Live poliovirus prepared from Sabin strains has also been used on a large scale in the USSR, Czechoslovakia, Bulgaria, Hungary, the German Democratic Republic and Albania, as well as in the Republic of Viet Nam and on a limited scale in China. In the USSR, a mass vaccination programme was instituted early in 1959 and by the end of the year over 15 million people had been vaccinated. During 1960 the programme was extended to cover the whole population between the ages of 6 months and 20 years, and within the first 5 months some 50-60 million persons were vaccinated. In the Baltic republics, where mass vaccination was performed during the first three months of 1959, the antibody conversion rate 3 months after vaccination was 94-98% to all three types of virus. Similar conversion figures were obtained in other regions. Reactions occurred in less than 3 per 100 000 vaccinated persons and were always mild, consisting mainly of transient fever, nausea, vomiting and intestinal symptoms. There was no evidence of an increase in cases of poliomyelitis during the 4-5 weeks following vaccination. On the contrary, in the Baltic republics there was a striking drop in incidence and poliomyelitis almost disappeared. In all areas where the vaccination programme was completed before the anticipated seasonal rise in incidence, this did not occur.

Using similar vaccines, about 3.5 million children have been vaccinated in Czechslovakia, 2.5 million in Hungary, 2.2 million in Bulgaria, 1.5 million in Viet Nam, and some tens of thousands in the German Democratic Republic and China. The final results were not available to the Expert Committee, but no complications had been reported.

A mass immunization programme with a vaccine prepared from Koprowski strains was started in Poland in October 1959 and completed in April 1960. Serological conversion rates of 89-100% were observed and epidemiological results are awaited.

Other trials with live poliovirus vaccine have been made in southern Africa, Florida (USA), and Singapore. In the island of Mauritius an epidemic due to type 1 virus terminated abruptly after 195 000 out of 212 000

children under 10 years of age had been given the corresponding type of vaccine within 3 days. Although the epidemic appeared to be already on the wane when the campaign was begun, vaccination seems to have brought it to an end more quickly. In Singapore, Sabin type 2 virus was administered to 199 000 children in the face of an epidemic due to type 1. It appears to have afforded considerable protection.

Safety of live vaccines

In almost all the trials with live vaccine carried out so far, untoward post-vaccinal reactions have been absent or insignificant and there has been no evidence that cases of poliomyelitis have been induced either directly or indirectly by administration of the attenuated virus. On present evidence, the fear of harmful effects due to the spread in the community of the progeny of the vaccine virus also appears to be unfounded. While these results have increased confidence in the use of attenuated viruses, the Expert Committee believed that further data must be accumulated before the unlimited use of live vaccines can be recommended without reservation. One of the most important questions still to be answered is how a true measure of safety can be devised and the possible clinical risks determined from field trials. A first requisite is that surveillance measures should be put into operation at the start of a vaccination programme and continued for 6-8 weeks after the programme has been terminated. While close surveillance is relatively simple in the case of small field trials involving not more than 500 persons, it becomes increasingly difficult with larger trials, and as more and more people are vaccinated the problem of finding a suitable unvaccinated control group grows more acute each year. If the surveillance measures cannot embrace every participant in the vaccinated and control groups it is essential that adequate sampling techniques should be employed.

Where trials are carried out at a time when cases of poliomyelitis are occurring in the district, it may be difficult to determine the true significance of post-vaccinal infections of the central nervous system. The Committee believed that all cases of poliomyelitis beginning within 5-30 days after ingestion of the vaccine should be investigated to determine whether they are due to the vaccine virus. This might be established with the aid of specific genetic markers to identify the particular strain isolated from the patient, but so far differentiation by this method has not proved very easy in practice. On this subject much more research is needed.

Special safety problems arise in connexion with the immunization of certain groups, such as premature or newborn infants, or pregnant women. Infection of the alimentary tract accompanied by virus excretion is readily obtained in newborn babies; in order to ensure a satisfactory immunological response, however, it may be advisable to delay vaccination until the age of 3 months. The Committee recommended that caution should be observed in administering live poliovirus vaccines to persons undergoing treatment with corticosteroids or surgery of the oropharynx, and that elective surgical procedures, including tonsillectomies and adenoidectomies, should not be performed on persons who have recently been given oral vaccine. There is no evidence so far, however, that injections given to vaccinated persons are likely to provoke poliomyelitis. In the USSR, the following were admitted as contraindications to the use of live vaccines: acute febrile states or other evidence of acute illness during the 2 weeks preceding the date set for vaccination; diarrhoea; intestinal disorders; tuberculosis; decompensated cardiovascular disease.

Attenuated viruses effective in producing a high level of serological responses have been found to spread readily to intimate family and household contacts, particularly in the lower socio-economic groups where hygiene is often poor. On the other hand, extra-familial spread does not appear to have been extensive and the attenuated polioviruses do not seem to persist in a community after mass immunization. The fear has been expressed, however, that a vaccine virus might gain in virulence in the course of multiple human passages and give rise to an epidemic of poliomyelitis in a

neighbouring country where the vaccine has not been used. Although there is no evidence that this is a real danger, the possibility cannot at present be discounted. More information on these questions is needed, especially with regard to the effect of different conditions on spread. It is important also that there should be co-operation between neighbouring states with regard to vaccination programmes and that the timing of such programmes should be co-ordinated. The Committee was of the opinion that such co-ordination might be best effected through WHO.

Live poliovirus vaccines have the great advantage of being cheap to produce and easy to administer. A disadvantage is the need to avoid contamination with extraneous viruses derived from monkey tissue. The Committee laid down a number of guiding principles for the manufacture and testing of live vaccines and strongly recommended that a WHO study group should be convened to draft international requirements. It also recommended that the study of simian viruses should be intensified, particularly with regard to their pathogenicity for man and methods of differential inactivation in live poliovirus vaccines.

Efficacy of live vaccines

" Take rates " after live poliovirus vaccination can be estimated either by virus isolation or by serological conversion. It seems to be generally accepted that a valuable measure of the immunizing capacity of a vaccine is the antibody response in persons who previously had no demonstrable antibodies to any of the three types of virus. The Committee recommended that, in the case of a monovalent vaccine, at least 25 triple negatives should be examined before and 1-2 months after vaccination; if a trivalent vaccine is used, the number examined should be about 50, or even higher if other interfering viruses are known to be present in the community. The Committee emphasized the importance of selecting the sample on sound statistical principles.

Agreement has not yet been reached regarding the significance of the appearance of antibodies at the lowest demonstrable level. It has been assumed that for a monovalent vaccine to be considered effective it should induce antibody formation in at least 90% of susceptible subjects. A response of this order has been achieved in many trials with most of the strains studied. The best evidence of an increased resistance to natural infection is considered to be excretion of virus by the vaccinee associated with a rise in antibody level. The average duration of virus excretion is 4-6 weeks, but it may continue as long as 3 months. Sometimes it is unaccompanied by the development of demonstrable antibodies, particularly in children under 3 months of age.

Ultimately, the efficacy of live poliovirus vaccines will have to be judged by their ability to control or prevent paralytic poliomyelitis. Although they have not yet been in use sufficiently long to yield conclusive data, some of the field trials discussed earlier in this article have already given encouraging results. A marked difference in morbidity between vaccinated and unvaccinated groups has been observed, and in some areas there has been a striking change in the seasonal incidence of poliomyelitis: after vaccination, incidence was lowest in the second half of the year, a time when it reached a maximum in previous years. The best results have been obtained when immunization was performed during the interepidemic period.

Choice of strains

Three sets of strains—Sabin, Koprowski and Lederle—have been tested extensively in the field, but the conditions under which they have been used have varied greatly and no attempts have been made to compare different strains under identical conditions. The Committee was therefore not in a position to make definite recommendations regarding the acceptability for general use of the different sets of vaccines at present available, but it suggested that selection should be based on the following criteria: low neuropathogenicity for monkeys; good immunizing effectiveness; genetic stability on human passage; lack of paralytogenic properties in man; restricted capacity to spread; and reduced capacity to invade tissues remote from the alimentary tract. The importance of certain

of these properties has not yet been satisfactorily assessed, however, and a good capacity to spread is considered by some to be a desirable property resulting in a high level of immunizing effectiveness for the community. The Committee was of the opinion that neurovirulence for monkeys is the only property that has been adequately studied on a comparative basis, although it is still not known to what extent it reflects human pathogenicity. As far as this property is concerned, the three Sabin strains appear to approach most closely to the optimum, and they also show good immunizing effectiveness. The question of the genetic structure and stability of polioviruses is of the greatest practical and theoretical interest, and the Committee recommended that research in this field should be furthered by all available means.

The criteria given above also apply to the selection of new strains for inclusion in vaccines. Reference has already been made to the use of genetic markers for the identification of strains; it is hoped that it will also be possible to use certain of these markers to assess neurovirulence since they exhibit variations that are correlated to some degree with changes in neuro-pathogenicity for monkeys. Although this method is not yet sufficiently reliable, a search is being made for further markers to increase its usefulness. After preliminary laboratory tests, the first field trials with a new strain should ideally be restricted to persons without natural antibody but who have been successfully immunized with inactivated vaccine. If preliminary tests with the new strain yield satisfactory results, strictly controlled tests may be carried out on gradually increasing numbers of fully susceptible children, and later on higher age-groups. Large-scale studies should be initiated only after controlled tests in several hundred persons have been conducted without incident.

Further studies are needed on the development of post-vaccinal viraemia. The clinical significance of viraemia following vaccination with live poliovirus is not yet known, but information on the degree of viraemia produced by different strains of the same type would be useful in selecting the strains most suitable for the manufacture of vaccines.

Public health aspects

The choice of inactivated or live virus vaccine for large-scale immunization programmes will depend upon the economic circumstances of the country concerned, its previous experience in the manufacture and distribution of poliovirus vaccines, and the epidemiological status of the population. Whichever type of vaccine is used, serological surveys will play an important part in the vaccination and surveillance programme. Their applications include: preliminary assessment of the immunological status of the population; testing of batches of vaccine for potency; and evaluation of the performance of a vaccine in the field, as already described.

The Committee was prepared to recommend without reservation that live virus should be used for the vaccination of communities where poliomyelitis is essentially a disease of infancy and early childhood. Most members felt, however, that where more than 20% of paralytic cases occur in persons over 15, the presence in the community of such a high proportion of vulnerable, non-immune adults necessitates caution in the use of live vaccine and careful surveillance until it has been established that it produces no significant harmful effects. There is a strong case, however, for using live vaccine in the face of epidemic poliomyelitis, when the risks of natural infection far outweigh the possible hazards from the use of live vaccine.

The Committee also recommended the use of live vaccine for its " booster " action and to induce intestinal immunity in countries using inactivated vaccine for primary immunization. As experience with live virus vaccine accumulates some of these countries may decide to change to the exclusive use of live vaccine, once the vulnerable adult section of the population has been effectively immunized.

One important outcome of the development of live virus vaccines is that it opens up the prospect of the eventual eradication of poliomyelitis. Before eradication can be attempted, further intensive epidemiological investigations of poliomyelitis in different regions of the world will be necessary, but the Com-

mittee considered the whole problem worthy of the closest study, both as a theoretical exercise and as a practical possibility.

One of the difficulties confronting public health authorities when using live vaccines is interference with the establishment of intestinal infection owing to the presence of other enteroviruses. This has been repeatedly encountered and it has been reported that it can be overcome by larger doses of vaccine, by repeated administration, or by rapid mass immunization. When trivalent vaccines are used, interference may also occur between the different strains of poliovirus, but this is not considered an argument against the use of trivalent vaccines. In some instances, however, a carrier state may completely prevent the multiplication of a vaccine strain.

Knowledge of enteroviruses has greatly increased during the past three years and they have been shown capable of producing a wide range of clinical pictures, some of which are liable to be confused with poliomyelitis. The most widely distributed are the Coxsackie group A viruses, of which 24 distinct immunological types have been recognized so far. Coxsackie A types 1, 2, 4, 5, 6, 7, 9, 10, 14, 16 and 23 have been incriminated as causing aseptic meningitis or meningoencephalitis, and others are under suspicion. There is also evidence that Coxsackie A virus may be the causative organism in some cases of infectious polyneuritis (the Guillain-Barré syndrome). Among the Coxsackie group B viruses 6 immunological types have been recognized. They cause a number of syndromes, including meningoencephalitis occasionally associated with mild and transient weakness and paralysis. The ECHO viruses types 4, 6 and 9 have also been held responsible for several sharp outbreaks of meningoencephalitis and aseptic meningitis.

It seems likely that the increasing incidence of enterovirus infections in adults and older children is a reflection of improved hygiene and a decreasing incidence in earlier age-groups. This trend may therefore be expected to continue, and it is possible that as the older age-groups are affected the diseases caused will become more severe. The Committee recommended that the study of these infections should be extended, particularly with a view to maintaining a sound classification. It was noted that WHO had initiated a programme to make available authentic strains of enteroviruses and eventually reference preparations of sera. An International Reference Centre and a number of regional centres are being designated to co-ordinate this work and to accept for final identification strains of enterovirus of clinical or epidemiological significance. It is hoped also to accumulate epidemiological and clinical information on the importance, distribution, serological variation, and paralytogenic properties of the enteroviruses.

Air pollution

Air pollution is a source of economic loss, a social evil and a menace to public health. Economic loss from air pollution, including damage to buildings, metal, fabrics, etc., has been estimated to be some £250 000 000 per year—about 4% of the national budget—in the United Kingdom alone. In the same country, where many towns are subject to heavy pollution, the mortality from chronic bronchitis is forty times greater than in Denmark, though other factors, including smoking habits, may also contribute to this situation.

A monograph entitled *Air Pollution*, in which current knowledge on the subject is summed up by an international group of experts, is about to be published by WHO and will be on sale early in 1961.

CHAGAS' DISEASE

Chagas' disease (American trypanosomiasis) is an infection caused by *Trypanosoma cruzi* and transmitted by various triatomes infesting human dwellings. Although it is known to exist throughout the Americas, except in Canada and perhaps Cuba, much remains to be discovered about its true incidence. Ignorance of the magnitude of the problem is the main obstacle in the way of organizing and indeed justifying suitable control programmes in countries where mortality and morbidity from other diseases are apparently greater. A Study Group on Chagas' Disease [1] was recently convened by the Pan American Sanitary Bureau, which acts as the WHO Regional Office for the Americas, and its report has now been published.[2]

Epidemiological aspects

Although there are so far no statistics on the prevalence of Chagas' disease in the various American countries, the group roughly estimated, on the basis of existing information, that at least 35 million people are exposed to the risk of infection with *T. cruzi*. If it is assumed, on the basis of the epidemiological surveys carried out in several countries, that the average infection rate is 20%, then at least 7 million people are infected. Infection of vertebrates, including humans, has been reported from all countries in the region stretching from the United States in the north to Argentina and Chile in the south.

Although Chagas' disease is more frequent in rural areas and small towns, autochthonous cases are also common in the peripheral zones of cities.

One of the more important vectors is *T. infestans*, which is widely distributed over South America, with infection rates varying generally from 20% to 30%. In the northern part of South America the principal vector is *Rhodnius prolixus*; in Panama, *R. pallescens*; in certain parts of Peru, *Panstrongylus herreri*, and in Mexico, some species of the *T. phyllosoma* group. Other widely distributed species are of less importance in maintaining Chagas' disease. It was reported that in some regions *Panstrongylus megistus* is closely adapted to human habitations, while in others it is prevalent around them.

Domestic animals, particularly dogs and cats, appear to be the most important reservoirs of *T. cruzi*. In some regions the cavy, or guinea-pig, is of special importance. The forest reservoirs seem to be of limited importance as sources of human infection.

Pathogenesis and anatomical pathology

T. cruzi is a parasite which multiplies primarily in cells of mesodermal or mesenchymal origin. This form of multiplication itself constitutes a fundamental biological fact in the life-cycle of this protozoan and in its pathogenic action, which is explained as due to a variety of mechanical, inflammatory, allergic and possibly toxic processes. Among other endogenous or exogenous factors, nutrition and variations in the virulence of different strains of parasite also seem to be of some importance in aggravating *T. cruzi* infection.

Symptomatology

Chagas' disease appears in two basic forms, one acute and the other chronic, with an intermediate phase between the two. The majority of the acute cases occur in young children or among recent arrivals in the endemic areas. The signs and symptoms of the acute forms vary greatly; apart from those observed at the portal of entry, there is usually fever, generalized adenopathy, slight enlarge-

[1] Members of the Study Group: Dr F. Biagi F., Mexico; Dr W. F. Cantrell, USA; Dr E. Dias, Brazil (Chairman); Dr G. de Freitas, Brazil; Dr A. Herrer, Peru; Dr C. M. Johnson, Panama; Dr A. R. Neghme, Chile; Dr J. L. Pedreira de Freitas, Brazil (Rapporteur); Dr F. Pifano C., Venezuela (Vice-Chairman); Dr T. Pizzi P., Chile; Dr C. F. Romaña, Argentina; Dr R. V. Talice, Uruguay. Secretariat: Dr N. Ansari, WHO (Joint Secretary); Dr A. N. Bica, PASB/WHO (Joint Secretary); Dr R. Huerta, PASB/WHO.

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1960, 202

ment of the liver and spleen, general infectious symptoms, cardiac enlargement, and various electrocardiographic changes. In the more severe cases there may be signs that the nervous system is affected.

The best known chronic forms are the cardiac ones, usually involving an increase in the size of the heart; electrocardiographic changes are frequent, and severe symptoms of cardiac insufficiency may occur. In addition to the cardiac forms, alimentary forms—particularly mega-oesophagus and megacolon—may, at least in some endemic areas, be manifestations of Chagas' disease in its chronic phase. Some observers have reported the existence of chronic neurological forms.

Mortality in the acute forms has been approximately 10% in certain regions; the lower the age-group, the higher the mortality rate, although fatal cases in adults have been reported. In the chronic forms the symptoms are so varied that many deaths are registered wrongly; the frequent sudden deaths from these forms are usually included among diseases of ill-defined or unknown origin.

Diagnosis

Etiological diagnosis in the acute phase is based on the detection of *T. cruzi* in the peripheral blood. This should be done by methods employing direct examination of blood or of stained smears; in some cases more sensitive techniques must be used, such as xenodiagnosis, inoculation of laboratory animals and blood cultures. The precipitin test is positive in a high percentage of acute cases. The agglutination titres of cultures are high in the acute phase, particularly if live *T. cruzi* cultures are used.

These methods have failed in almost all chronic cases, owing to the smaller number of parasites in the blood. Here indirect methods—for example, the complement fixation test—yield better results. It is most important to standardize the antigens and techniques used in this test.

In addition to cases which exhibit symptoms permitting clinical diagnosis of Chagas' disease there are many others without typical symptoms, in which a diagnosis can be established only by means of laboratory tests. Supplementary examinations, particularly by electrocardiography, radiological examination and, to a smaller extent, blood tests, can be of great value.

Control and prevention

The persistence of Chagas' disease is due primarily to badly constructed dwellings; these, in conjunction with primitive habits, favour the breeding of triatomes adapted to human dwellings. For the prevention of the disease, therefore, it is essential to improve housing and promote hygienic habits.

Some of the modern residual insecticides have proved effective against the triatomes. Gamma-BHC and dieldrin have proved to be the most effective. The highly toxic effect of the latter on man and domestic animals makes it difficult to apply and prevents its use in henruns and farmyards, which are important breeding places for some species of *Triatoma*. Moreover, in some areas it has been proved that dieldrin is not sufficiently effective against certain vectors. It has been demonstrated that BHC has satisfactory triatomicidal effects, without having the drawbacks of toxicity reported in the case of dieldrin. None of the residual insecticides so far tried has a lethal effect on triatome eggs. Sprayings should be very extensive and thorough, covering not only the internal surfaces of houses and their furniture and fittings but also outbuildings, where vectors frequently reproduce. It has been shown that a single spraying of dieldrin or BHC is insufficient to exterminate all the triatomes in a locality, and it has therefore been recommended that a second or even a third spraying be performed with intervals of 30-180 days between each spraying.

So far, resistance to insecticides has not been demonstrated in any *Triatoma* species. Despite the technical and administrative difficulties involved, it was recommended that the results of simultaneous *Triatoma* control and malaria eradication programmes should be studied.

Health education is most important. It should aim at spreading knowledge of the harmful activity of triatomes and convincing

the population that it is important to exterminate them.

The complement fixation test should be applied to blood donors as a matter of routine, not only in endemic areas but also in regions where people coming from endemic areas have settled, since it has been proved that Chagas' disease can be transmitted to man through blood transfusion. If it is impossible to apply the complement fixation test as a matter of routine, the addition of trypanocidal substances to the blood could be useful. The prevention of congenital transmission presents great practical difficulties, and it is necessary to study the conditions which may favour it.

The report concludes with recommendations on research, and stresses the importance of international co-operation in the control of the disease.

CIRRHOSIS OF THE LIVER IN FRANCE

An investigation was recently undertaken by the nutrition department of the Institut national d'Hygiène, Paris, into the role of alcohol in the etiology of cirrhosis of the liver in France. One of the participants [1] in a seminar on the application of epidemiology in health administration, held by the WHO Regional Office for Europe at Opatija, Yugoslavia, from 16 to 23 September 1960, presented the results of this investigation [2] as an illustration of the value of *ad hoc* epidemiological studies.

Cirrhosis of the liver is relatively more common in France than in the rest of Europe; the death rate in 1956 was the highest in western Europe (32.5 per 100 000 inhabitants, as against 2.6 in England and Wales and 13.6 in the Federal Republic of Germany). For many years the medical profession in France has attributed the high incidence of the disease to excessive consumption of alcohol, and statistics from hospitals agree that 80-85% of cirrhoses are alcoholic in origin. But the medical profession has been accused of prejudice, and wine merchants have put forward the argument that in a population of which 80% are drinkers it could be maintained that practically all illnesses are alcoholic in origin. It is true—the argument proceeds—that the average consumption of wine in France (approximately 0.7 of a litre per adult per day, the strength of the wine being calculated at 80 grams of alcohol per litre) is much higher than elsewhere, and that the mortality from cirrhosis of the liver is also much greater; but this might be merely coincidence, and the average consumption of alcohol, though high, is much less than would be needed to cause cirrhosis.

The fallacy in the latter part of this argument is obvious. Clearly, if the average consumption is 0.7 of a litre per day some people drink less than this amount and some more, and it is only among those who drink more that cirrhosis is alleged to appear when it is of alcoholic origin; indeed, French doctors maintain that two to four times as much alcohol as this average must be ingested to cause cirrhosis. But there was not enough factual evidence to show this. All that could be argued was that when the consumption of alcohol fell during the Second World War the death rate from cirrhosis of the liver also fell: a piece of presumptive evidence that was far from being universally accepted.

The nutrition department of the Institut national d'Hygiène sought to settle the matter by a survey designed to answer five questions. These were as follows: did persons believed to have cirrhosis of alcoholic origin drink more before their illness than random controls of the same age, same sex and same social environment without cirrhosis; were they less well nourished (i.e., is cirrhosis due to alcohol or to an associated nutritional deficiency); is the reduced food intake so often seen when cirrhosis becomes decompensated a cause or a consequence of the decompensation; can the amount of alcohol that causes cirrhosis be

[1] Dr G. Péquignot, Deputy Head of the Department of Nutrition, Institut national d'Hygiène, Paris

[2] Unpublished working document EURO-187/10

determined; and what part does wine play in the alcoholism of cirrhotics?

The survey was carried out in hospitals in Paris, Marseilles and Nantes, all patients with alcoholic cirrhosis being questioned and a non-cirrhotic control being chosen at random in the same department for each patient questioned. The physical activity at work and outside work, the height and the usual weight before cirrhosis began were recorded, and a detailed food questionnaire was devised to establish the daily food intake before and after the onset of the disease, as well as the quantity of alcohol absorbed daily. In addition, questions were asked to reveal the social background: about the patients' family and parents, income, living conditions, and standard of living.

In all 116 cirrhotics and 116 controls were compared. They did not differ significantly in age, physical activity, weight, or calorie or protein intake; but the alcohol intake of the cirrhotics was found to be approximately 2.5 times greater than that of the non-cirrhotics. Before they fell ill, the cirrhotics had been just as well nourished as the others; consequently, it was concluded, cirrhosis cannot be attributed to dietary deficiencies.

The table below classifies the patients and the controls according to the amount of alcohol ingested:

	Cirrhotics	*Controls*
Less than 80 g	1	59
From 80 to 160 g	51	50
More than 160 g	64	7
Total	116	116

Only one out of the 116 patients with cirrhosis said that he had consumed less than 80 grams of alcohol (i.e., less than 1 litre of wine at 10°) daily. From this it may be inferred that alcoholic cirrhosis appears only when consumption of alcohol is greater than 1 litre a day. But 50 out of the 116 controls consumed 80 to 160 grams of alcohol a day (1 to 2 litres of wine), and it was only in the category from 160 grams (2 litres of wine) up that controls tended to decrease in number (7 out of 116), while more than half of the cirrhotics (64 out of the 116) came within this range.

It seems reasonable to infer that cirrhosis is likeliest when the intake is between 2 and 2.5 litres of wine a day (172 to 212 grams of alcohol). Cirrhosis can occur when it is 1 litre or more, but when it exceeds 2 litres the probability of its occurrence is much increased.

Is decreased food intake a decompensating factor in cirrhosis? Apparently not to any marked degree: in 88 cases out of the 116 it failed to cause decompensation; thus even at this late state the nutritional deficiency is only associated, not causal.

Finally, the survey established that wine represented 80-90% of the alcohol ingested.

What errors are possible in a survey of this kind? One is that the answers given are inaccurate, either because of observer error or because those answering the questions do not remember clearly, or deliberately understate, their alcohol consumption. Observer error can be allowed for by having the same person question both patients and controls. If the subject error is due to defective memory, mistakes will tend to cancel out if the number of subjects is large enough; but if it is due to deliberate falsification it may be cumulative. In a survey of the effects of alcohol on cirrhosis of the liver the likelihood is that patients will understate their consumption of alcohol. The survey has shown that cirrhotics consume 2.5 times more than non-cirrhotics, and if this is an underestimate it merely strengthens the conclusion that excessive consumption of alcohol is liable to cause cirrhosis. If it is an underestimate, of course, it also follows that the lower limits of the toxic dose may be fixed rather too low; but this is not a disadvantage.

The other possible objection to this survey is that the controls were taken from patients in the hospitals. They were, however, people of the same age, same sex, and same social background; they were chosen at random; they suffered from illnesses of different kinds; and all were interrogated about their intake of alcohol prior to their illnesses. As controls they therefore seem to have been suitable.

POSTAGE OF PERISHABLE BIOLOGICAL MATERIAL

On the ground that delays in the despatch and arrival of perishable biological material by post were frequent, to the detriment of the material and therefore of diagnosis and research, the International Association of Microbiological Societies asked WHO to consider the question of the unification of rules and regulations in this connexion. WHO took up the matter in collaboration with the Universal Postal Union, and after discussions at the Universal Postal Congress held in 1957 in Ottawa an article on the subject was inserted in the new Universal Postal Union Convention, which came into force on 1 April 1959.

This new article lays down that, for international postal transmission, perishable biological material is to be packed and labelled in a particular way, to be sent by letter post, and to be exchanged only between officially recognized laboratories. Moreover, this postal traffic may take place only between countries agreeing to it either on a reciprocal basis or as one-way traffic. Living animals and insects are not to be accounted perishable biological material.

Material containing living pathogenic micro-organisms must be inserted into a flask or tube of thick glass or an ampoule, securely corked or sealed so as to be airtight and waterproof after closure. This container must be wrapped in thick absorbent material such as cotton-wool, rolled several times round the container and tied above and below it to form a spindle-shaped bundle which is then placed in a strong metal case and tightly closed. There should be enough absorbent material between the inner container and the case to absorb the liquid contents or any liquid that may form if the inner container breaks. The metal case should be so constructed and closed as to make contamination on the outside impossible, and should itself be wrapped in absorbent material and placed in an outside container so that it is not loose. The outside protective container must be of solid wood or metal or of material of equivalent strength; and possess a lid that cannot come open in transit. Special precautions (e.g., freeze drying or packing with ice) must be taken to preserve the material if it is sensitive to high temperature; and if it is being carried by air the packing must be strong enough to resist variations of atmospheric pressure.

It is also specified in the new article that the outside container, or its outer cover, if any, must bear, along with the addresses of the officially recognized despatching and receiving laboratories, a violet label with a special symbol and the following notices in French, the official UPU language: " *Cette étiquette ne peut être utilisée que par les laboratoires officiellement reconnus* " (" This label can be used only by officially recognized laboratories "); " *Matières biologiques périssables (à usage médical)* " (" Perishable biological material—for medical use "); " *Dangereux : ne pas ouvrir pendant le transport* " (" Dangerous: not to be opened in transit "); " *Sans valeur commerciale* " (" Of no commercial value "); and " *Emballé selon les règles postales internationales de sécurité* " (" Packed according to international postal safety regulations ").

Perishable biological material that does not contain living pathogenic micro-organisms must be packed in a waterproof container and have an outer protective container as well; and there should be absorbent material either in the inner container or between the inner and outer containers to absorb all the liquid contained or likely to form if the inner container is broken. The contents of both containers should be so packed that they are not loose. The same precautions must be taken as for material containing pathogenic micro-organisms to protect the contents from high temperatures or from variations in atmospheric pressure;

and the same label must be affixed, with the same notices (except for those dealing with danger and opening in transit).

WHO and the Universal Postal Union have agreed on the form of the label and the wording to appear on it. National postal administrations can obtain stocks of the label from the headquarters of the Universal Postal Union, Berne, Switzerland, or, if they wish, purchase them from WHO direct.

Another question on which WHO and the Universal Postal Union are collaborating is that of the definition of " officially recognized laboratories ". In a circular letter to Member States, WHO has suggested that these might include laboratories directed or supported by governments, local authorities or universities, or licensed commercially or otherwise to produce biological products and to carry out biological research, or any others that the competent authorities consider entitled to use the label established by the new Convention.

It is to be hoped that the regulations that have now been framed will solve the difficulties that led the International Association of Microbiological Societies to seek clarification and unification of the postal rules in force. All those engaged in public health work or international medical investigations who make use of the postal services for the international transport of perishable biological material should inform WHO of any difficulties they experience under the new regulations and of any improvements they think desirable.

Health Legislation

Iodine prophylaxis of endemic goitre

Experience has shown that iodine deficiency is the essential etiological factor in endemic goitre. At first sight, therefore, it is surprising to find that only a few countries have made iodine prophylaxis compulsory. The example of Switzerland, where iodine prophylaxis was introduced more than thirty years ago, has not been followed to any extent, not because of any shortcomings in the method, but because of technical, political or economic difficulties. In certain countries, only coarse unrefined salt is used, and this is difficult to iodize. Furthermore, climatic conditions may render iodized salt unstable. It is difficult to convince the legislative authorities that there is real justification for introducing iodine prophylaxis when there are other health problems demanding priority. Financial considerations are also involved: the iodization of salt requires special equipment, iodine compounds are expensive and so is the specialized staff required for proper mixing. But the main reason why iodine prophylaxis is not more widely used is probably that, in many countries, no systematic surveys of endemic goitre have been made until quite recently.

Such surveys show that endemic goitre is present to a greater or lesser extent in some 100 countries and territories, but of these only about ten have adopted legal measures to combat the disease. In Austria, the USA and the United Kingdom, scientific committees have recommended the introduction of iodized salt, but their recommendations have not been followed up by legislation.

In some countries iodine prophylaxis is applied on a purely optional basis or left to the initiative of the health authorities. However, experience has shown that legislation is the only rapid way of ensuring sufficient consumption of iodized salt to eliminate endemic goitre.

The WHO *International Digest of Health Legislation* has just published a survey of legislation on the prophylaxis of endemic goitre by iodine.[1] The use of iodized salt was

[1] See *Int. Dig. Hlth Legis.*, 1960, **11**, 387-398. This study is also available in pamphlet form (price: 1/9, $0.30, or Sw. fr. 1.—). It is a slightly modified version of a survey published in *Endemic Goitre* (*World Health Organization : Monograph Series*, No. 44).

first made compulsory in 1924 (Nidwalden and Vaud, Switzerland). Between then and 1950, similar legislation was introduced in Canada (1949), Costa Rica (1941), Hungary (1948), Mexico (1942) and the Netherlands (1942). However, the majority of the existing regulations on the iodization of cooking salt and other methods of prophylaxis by iodization have been introduced since 1950. The only countries making the use of iodized salt compulsory throughout the national territory are Canada, Colombia, Costa Rica, Guatemala, Panama, Paraguay and Yugoslavia. In Switzerland, where health measures are on the cantonal level, the use of iodized salt is compulsory in most of the cantons, whether goitrous or not.

In Brazil, Bulgaria, Hungary, Mexico, the Netherlands and Peru, the legislation covers only the goitrous areas. The Chilean legislation authorizes the introduction of iodized salt but does not indicate that its use is compulsory.

The most commonly specified method of remedying iodine deficiency is the iodization of kitchen salt. In 1953, the WHO Study Group on Endemic Goitre recommended that "food salt" be iodized in the proportion of 10 mg per kg on the basis of a daily salt consumption of 10 g. It was agreed, however, that this proportion might be varied according to circumstances, and in fact the proportions prescribed in some countries are different.

The regulations may provide for certain exceptions. Thus, as far back as 1924, in the Swiss cantons where iodization of salt was compulsory, non-iodized salt could be obtained on presentation of a medical certificate and at the express wish of the person concerned. In Costa Rica and Panama, pharmacies may sell non-iodized salt to persons presenting medical certificates.

In some cases, the regulations provide for supervision of iodization factories and installations and for the analysis of samples of iodized salt to check whether they contain the stipulated amount of iodine. In Brazil, for example, factories have to be inspected every two months and salt samples taken at each inspection. In Bulgaria, iodized salt must be analysed every two months. Requirements are similar in the USSR where the instructions also provide that each consignment of salt be accompanied by a certificate indicating the iodine content. If difficulties arise during transport or if the packing is defective, the salt must also be analysed on arrival. Salt samples are taken by representatives of the health and epidemiological services of the USSR Ministry of Health or by the authorities in charge of goitre control. In Guatemala, the General Association of Salt-Makers is authorized to inspect private factories preparing the salt and is responsible for notifying the health authorities of any fault, deficiency, or irregularity and for taking the measures necessary in each case to remedy such defects. The Public Health Administration may also order the inspection of factories by departmental delegates or health inspectors in order to ensure that the salt is being correctly iodized. In Peru, supervision is entrusted to the medical officers in charge of the health units of the departments where the State salt enrichment factories are situated. These factories are required to report each month to the Department of Endemic Goitre the quantity of salt that has been iodized and to supply samples taken at both the factory and the place of distribution.

Some regulations include conditions governing the packing and labelling of iodized salt offered for sale. In Bulgaria, fine iodized salt for retail sale must be packed in containers made of parchment paper and cardboard; salt for wholesale supply must be in a triple wrapping. In a number of countries, the iodine content, the date of production, the name of the factory and the net weight must be indicated on the wrapping.

There are few regulations containing provisions to facilitate the preparation and distribution of iodized salt. In Brazil, the Ministry of Health facilitates the importation of sodium iodide or potassium iodide, and supplies it at cost price to firms preparing iodized salt. In Guatemala, the General Association of Salt-Makers transmits to the competent authorities the necessary applications for exemption from customs duties, etc. in order to facilitate the purchase of iodization equipment.

Notes and News

Regional Committee for the Eastern Mediterranean

Sub-Committee A of the tenth session of the WHO Regional Committee for the Eastern Mediterranean met in Tunis from 15 to 19 August 1960, and Sub-Committee B met in Geneva from 24 to 26 August 1960.

Sub-Committee A elected the following officers: Dr Ahmed Ridha Farah (Tunisia), Chairman; Dr A. A. Zaki (Sudan) and Dr A. Nabilsi (Jordan), Vice-Chairmen. Dr S. Syman (Israel) was elected Chairman of Sub-Committee B, and Mr H. Sebsebie (Ethiopia), Vice-Chairman.

The resolutions adopted by the two Sub-Committees on subjects common to both agendas were identical.

In his annual report, Dr A. H. Taba, WHO Regional Director for the Eastern Mediterranean, stated that a quarter of the budget for the Region was now being spent on education and training. More than 1400 fellowships had been granted—217 in 1959, as compared with 32 in 1949—to health workers from the Region. More and more of these fellowships—one out of two in 1959—were for studies in the Region itself. The chief subject of study was public health administration, followed by environmental sanitation, nursing, maternal and child health, malaria eradication, and tuberculosis control. Of 129 professors and teachers assigned by WHO in 1959 to 27 different countries and territories, 51 were assigned to 11 countries and territories in the Eastern Mediterranean Region.

WHO-assisted malaria eradication campaigns were in operation in 11 countries and territories containing 84% of the population at risk in the Region. In 1959, 17 million persons in 6 adjacent territories had been protected against the disease. The eradication of malaria from the Region had become all the more urgent because of the development of insecticide resistance among vector mosquitos in certain areas. The success of the programme was also threatened by the danger of the reintroduction of infection by nomadic groups, and close co-ordination of programmes in neighbouring countries was therefore essential.

Smallpox had declined markedly in the Region during 1959; only 6262 cases had been reported in Pakistan, as compared with 47 897 in the "epidemic year" 1958, and 24 724 in 1957. The decline in the disease was particularly marked in the countries where mass vaccination campaigns had been carried out. Dried vaccine had proved its value in these campaigns, and five laboratories, set up with help from WHO, were already producing it in different countries of the Region. A WHO expert team had recently visited 9 countries to report on smallpox control activities and to estimate possibilities of eradication in the near future. The team considered that, with a special effort, eradication of smallpox from the Region could be achieved within four or five years.

Referring to bilharziasis, which is endemic in 11 countries of the Region, Dr Taba spoke of the urgent necessity of intensifying research on the snail vectors of bilharziasis, molluscicides, chemotherapy and chemoprophylaxis of the disease, and agricultural practices favouring its spread. Another communicable disease of particular importance in the Region is trachoma; research workers at the WHO-assisted Ophthalmological Centre in Tunis had succeeded in isolating the trachoma virus and were now attempting to produce an antitrachoma vaccine.

Other problems reviewed by Dr Taba included rural sanitation and the provision of safe water supplies, health problems of urbanization, nutrition, industrial medicine, protection against radiation, and mental health in relation to social and economic change.

From the discussions on Dr Taba's report, it was clear that the majority of countries in the Region had made advances in health during the year under review, and that integrated and co-ordinated public health services were an important feature of their long-term plans. As regards

education and training, it was considered that auxiliary personnel should be recruited and trained with a view to their absorption into the general public health services rather than for specialized tasks. The need to continue assistance to medical faculties was generally stressed. An evaluation of the fellowships programme had been made, and it was considered that this would be extremely helpful in formulating future plans. The general trend towards inter-country and inter-regional activities was commended.

Although the malaria and smallpox eradication programmes were progressing favourably it was felt that there was room for improvement in inter-country co-operation and legislation in connexion with these programmes. Participants also felt that research on trachoma, bilharziasis, tuberculosis, leprosy and onchocerciasis should be intensified.

It was urged that work in paediatrics should be strengthened, that nursing curricula should include social medicine, public health and mental health courses, and that the influence of nomadism on health problems should be studied.

The proposed programme and budget estimates for 1962 were endorsed by the Committee. They provided for the use of about $2 000 000 from the regular WHO budget, as well as $1 000 000 from United Nations Technical Assistance funds and approximately the same amount from the Malaria Eradication Special Account. A supplemental Technical Assistance programme for Cyprus and Somalia was approved.

Resolutions were adopted urging governments to promote more effective mental health services, recommending further study of leishmaniasis and its addition to the list of notifiable diseases in the Region, and urging Member States to organize special departments on radiation control in their respective Ministries of Health.

Both Sub-Committees held technical discussions on "Tuberculosis control with particular reference to domiciliary treatment". The participants in the discussions recognized that tuberculosis remains one of the principal medical and social problems in the Eastern Mediterranean Region. They recommended that control programmes be made simpler, more economical and more effective, utilizing BCG vaccine and antimicrobial drugs for prophylaxis and therapy, and that the emphasis in these programmes be on domiciliary chemotherapy. "Solar radiation and its related heat effect on the human organism" was selected as the subject of the technical discussions in 1962. Next year's subject is "Poliomyelitis".

Sub-Committee A decided to hold its 1961 meeting in Lebanon, and its 1962 meeting in Saudi Arabia.

Anaemia in Mauritius

Anaemia has been a considerable public health problem in Mauritius for many years—affecting about 56% of the entire population in 1956—and it has been attributed variously to hookworm infection, malnutrition, and malaria. Since 1952, however, malaria has been virtually eradicated from the island. In order to pin down the causes of the anaemia, which it was now obvious did not include malaria, the Government of Mauritius asked WHO to make a survey of the situation. This was begun in 1955, with interesting results that will shortly be published in the WHO Bulletin.[1]

Until the survey was begun it was generally held, on the basis of the findings of Sippe,[2] that the anaemia prevalent in Mauritius was nutritional macrocytic anaemia. It thus fell into the category of anaemias occurring among natives of tropical and subtropical regions, with a blood picture in typical cases similar to that of pernicious anaemia and characterized by macrocytosis, extreme poikilocytosis, leukopenia, relative lymphocytosis, and reticulocytosis; and so it was treated with yeast, vitamin B_{12}, or liver extracts. Sippe had stressed the importance of malaria in its etiology, pointing out that the maximal seasonal incidence of anaemia, from June to August, followed the peak incidence of malaria.

The main findings of the survey in blood film examination of cases of anaemia were hypochromia (95%) and microcytosis (84%), often associated with anisocytosis (64%) and poikilocytosis (42%). Macrocytosis, on the other hand, was rare (2%), and reticulocytosis was not a feature of the blood picture. When it was realized that the anaemia was usually hypochromic and

[1] Stott, G. (1960) *Bull. Wld Hlth Org.*, 23 (In press)

[2] Sippe, G. (1947) *Nutritional macrocytic anaemia*, London

microcytic, not macrocytic, it was judged probable that it would generally respond to treatment with iron preparations; and this proved to be correct in a trial with a series of 90 patients.

The success of this trial suggested that the problem of anaemia in Mauritius might be solved by adding iron to the diet of the population. A number of therapeutic trials were then carried out, not only with iron, but also—to test the possibility that defective nutrition and hookworm infection had something to do with the anaemia—with folic acid, dried skim milk, and anthelmintics. These substances were found to have no effect on the anaemia, but the iron brought about a steady rise in the haemoglobin level. It was accordingly recommended to the Department of Education in Mauritius that every child attending primary school be given a tablet of ferrous sulfate daily during school term. When this recommendation was accepted haemoglobin surveys were made in a school where anaemia was common, both before and after the scheme was introduced. The second survey, eight months afterwards, revealed a highly significant rise in the mean haemoglobin and a marked diminution in the incidence of anaemia—an improvement observed in boys and girls of all ages.

Further trials were carried out to ascertain the amount of iron required to bring about a satisfactory increase in haemoglobin levels, and it was calculated that initial enrichment of the diet with 10 mg of elemental iron per head per day would be adequate. This might be reduced progressively until a satisfactory maintenance dose was found.

The conclusion of the survey was that circumstances in Mauritius "appear suitable for the introduction of enrichment with iron of the national diet as a means of reducing the incidence and severity of hypochromic microcytic anaemia in the whole population". The mean calculated intake of elemental iron in a random sample of people from a village where anaemia was rife was found in the survey to be 6.3 mg per head per day, and estimates of the total food supplies available in the island in the years 1955-1957 indicated that the average diet supplied only 10.2 mg of elemental iron. These amounts are much smaller than those recorded in other tropical areas and would seem hardly sufficient to meet physiological requirements. The iron content of the diet is low, the author of the Bulletin paper thinks, because iron-rich foods are little consumed, a possible reason for this being that rice—an important item in the local diet—is so cooked that the iron it contains is lost. It is estimated that at least 37.5% of the population of Mauritius suffer from hookworm infestation leading to a chronic loss of blood. The failure of anthelmintics alone to raise haemoglobin levels during the trials is probably due to the absence of sufficient iron in the diet to restore haemoglobin levels after the hookworms are eradicated. The investigators were unable to attribute much importance to the loss of iron in sweat or to the state of protein nutrition among the islanders.

Teaching of radiation medicine

A short course on radiation medicine for teachers in medical schools was held by the Middlesex Hospital, England, from 31 August to 27 September 1960, at the invitation of the WHO Regional Office for Europe. It was attended by nine fellows from the following countries: Austria, Czechoslovakia, Denmark, Germany, Netherlands, Norway, Sweden, Switzerland, and Yugoslavia. All participants were experts in the field of radiation medicine and it is hoped that they will organize teaching courses for undergraduate students in their respective countries.

The course covered the following subjects: radiation physics and chemistry, including measurement of radioactivity; use of radioactive isotopes as a research tool in physiology, biochemistry and medicine; effects of ionizing radiations on animal and human tissues; genetic effects; use for diagnosis and therapy; disposal of waste products in laboratories, hospitals and industry; protection from hazards in industry; national disasters involving contamination of the environment. Special attention was paid to the use of teaching aids and to teaching methods, particularly those involving the participation of several disciplines, whether group discussions, combined lectures, or practical exercises.

The participants in the course visited a number of scientific institutes and research establishments, and took part in laboratory demonstrations and experiments suitable for the instruction of medical students at different stages of the curriculum. They also saw a selection of films on various aspects of radiation medicine.

Application of epidemiology in health administration

A seminar on the application of epidemiology in health administration was held by the WHO Regional Office for Europe in Opatija, Yugoslavia, from 16 to 23 September, with the participation of 23 public health administrators from 22 countries and an international panel of lecturers.

The seminar began with a full discussion of the value and limitations of the sources of data generally available to health departments for both communicable and non-communicable diseases. Additional epidemiological methods which might be used when these sources are inadequate to guide action were then considered. The following specific topics were introduced by lecturers and then generally discussed: the place and limitations of mortality data; the use of routine sources for mortality information; the organization of special registers for tuberculosis and cancer; survey methods and the use of sampling procedures; *ad hoc* epidemiological studies; assessment of the efficacy of control measures. During the seminar, participants paid a visit to the Health Centre in Rijeka.

Training in medical rehabilitation

A training course in medical rehabilitation started in Copenhagen on 3 October 1960, under the auspices of the WHO Regional Office for Europe and the Danish Government. It will continue until the end of June 1961, and participants will study in Denmark for the first eight months. The final month will be devoted to training in vocational and industrial rehabilitation in the United Kingdom.

The course is primarily for qualified physicians wishing to study medical rehabilitation either generally or in relation to a specialty such as geriatrics, orthopaedics, neurosurgery, rheumatology, etc. The social, vocational and industrial aspects of rehabilitation will also be dealt with, with the collaboration of the United Nations and the International Labour Organisation.

Both theoretical and practical instruction will be given in such fields as anatomy, physiology of the locomotor nervous systems, blood circulation, traumatology and psychology in relation to disability. Special topics will include psychotherapy, rheumatology, geriatrics, neurosurgery, orthopaedic appliances, organization of the rehabilitation team, vocational tests, psychometrics, etc. There will also be discussions and visits to rehabilitation centres. The course—which it is hoped to repeat in subsequent years—will conclude with an examination, and successful candidates will receive a diploma from Copenhagen University.

Eight fellows have been nominated to take part by the Governments of the following countries: Greece (1), Iraq (1), Lebanon (1), Spain (2), Turkey (1), United Arab Republic, Province of Egypt (1), and Yugoslavia (1).

International tuberculosis training course

Since 1953, WHO has supported, out of Technical Assistance funds, an international tuberculosis training course, given once a year at the International Tuberculosis Training and Demonstration Centre in Istanbul, Turkey. WHO recruits international lecturers for the course, and provides fellowships for physicians and nurses from countries eligible for technical assistance to enable them to attend.

This year's course was held from 26 September to 15 October, and as in previous years it dealt mainly with the preventive and social aspects of tuberculosis. It included lectures, demonstrations and discussions, and was attended by 17 physicians and nurses from the African, Eastern Mediterranean and European Regions.

Expert Committee on Mental Health

A WHO Expert Committee on Mental Health met in Geneva from 4 to 10 October 1960. One of its tasks was to review present resources in personnel and facilities for mental health work in the various countries of the world. An enquiry made before the meeting showed that these resources were in general inadequate. Out of 32 countries supplying information, only 4 have anything approaching the desirable proportion of one psychiatrist per 10 000 population. There are

also serious shortages in psychiatric nursing personnel, and even in highly industrialized countries there are psychiatric hospitals without appropriately trained staff.

The Committee devoted much time to considering types of research, both national and international, which must be given priority if further advances are to be made in preventing mental illness. These included investigations into brain function, social attitudes, effects of cultural change, psychoses of the aged, effects of nutrition, and genetic factors.

An account of the Committee's work will appear in the Chronicle when its report is published.

European seminar for sanitary engineers

Some 50 sanitary engineers and administrators of national environmental sanitation programmes from 23 European countries took part in the seventh European seminar for sanitary engineers sponsored by the WHO Regional Office for Europe and held, from 6 to 13 October, at Ciudad Universitaria, Madrid, in co-operation with the Spanish Government.

Previous seminars, including those at Rome (1951), London (1952), Opatija (1954), Helsinki (1956), and Nice (1958), discussed the training and functions of sanitary engineers, water supply and purification, sewerage and sewage treatment (both domestic and industrial), solid waste or refuse disposal, prevention of water and air pollution, standards for drinking water, biological and chemical relationships, housing sanitation, and the increasing use of radioactive substances.

The main theme of this year's seminar was research needs in sanitary engineering, and the measures which should be taken to meet such needs by governments, research institutes, universities and technical schools, and industrial or municipal establishments. It is recognized that present-day methods of sanitary engineering, however successful, are still too empirical and based on insufficient knowledge. The resulting high costs and inefficiency tend to make sanitary improvements less accessible to large groups of the population, particularly in rural areas. In the urban areas, current methods are becoming less and less effective in dealing with such growing problems as water and air pollution.

The seminar also discussed the treatment of small community sewage wastes, a field of great interest and importance in Europe and one in which considerable technical progress has been made in recent years, and sanitary engineering requirements of atomic energy developments.

Fourteen working papers were presented by experts from Czechoslovakia, the Federal Republic of Germany, the Netherlands, Spain, Switzerland, the United Kingdom, the USA and the USSR, and by WHO technical staff.

Regional training course on vital and health statistics

A regional training course on vital and health statistics was held at the WHO Regional Office for the Western Pacific, Manila, Philippines, from 17 October to 25 November 1960, with the co-operation of the United Nations. Its aim was to help Member States improve their civil registration and vital and health statistical services, so that the data produced may fulfil national needs and meet the criteria of international uniformity and comparability. As population estimates between census years are based on vital statistical data, it is essential for the countries and territories of the Region to be able to furnish reliable vital statistics in the years following the 1960-61 census.

The programme of the course was designed to provide members of national statistical services with additional training in the organizational, methodological and analytical techniques and practices of vital and health statistics; to give them an opportunity of exchanging information and ideas; to review the uses of statistics in health programmes; and to develop uniform methods and minimum requirements for national vital and health statistics.

Lectures, followed by group discussions and laboratory exercises, were given on the following topics: vital statistics methods; health statistics methods; analysis and sample survey methods, with special emphasis on administrative and methodological problems. A demographic and health survey was conducted near Manila during the course, and field visits were held so that par-

ticipants might study the operation of national, provincial and local vital and health statistics services in the Philippines.

The course was attended by 40 statisticians from Burma, China (Taiwan), the Federation of Malaya, Guam, India, Iran, Japan, Korea, the Philippines, Portuguese Timor and Viet Nam.

Pulmonary heart disease

A WHO Expert Committee on Pulmonary Heart Disease met in Geneva from 10 to 15 October 1960. The aims of the Committee were: to define chronic pulmonary heart disease (cor pulmonale) in terms useful for further discussion; to provide a tentative classification; to describe in broad terms the pathophysiology of cor pulmonale and to establish criteria for diagnosis; to consider principles for treatment and prevention of the causative diseases; and to present suggestions for future research.

An account of the Committee's work will appear in the Chronicle when its report is published. It is hoped that this report will help to dispel present confusion concerning this condition, on which there has hitherto been no agreement about terminology, definition or classification.

Quarantinable diseases

The Committee on International Quarantine meets annually to review the functioning of the International Sanitary Regulations and their effect on international travel. This year's meeting was held in Geneva from 17 to 22 October.

The Committee noted that, although there has been a decline in the incidence of the six quarantinable diseases in the past four years, with a corresponding reduction in mortality, there has been little change in their distribution throughout the world.

Cholera, which is usually present only in East Pakistan and some parts of India, appeared in Burma, West Pakistan and Afghanistan in 1960. For more than 30 years, this disease has been confined to Asia, except for the 1947 epidemic in Egypt. Deaths from cholera in India and Pakistan have been steadily declining over the past 15 years.

Many foci of wild rodent plague still persist in Asia, Africa and the Americas, so that there is a constant danger that the disease may spread to rats in villages and towns. The annual average number of deaths from plague dropped from 170 300 in the years 1919-28 to less than 200 in 1954-58. In 1959 a total of only 83 deaths was registered in 10 countries.

The main focus of smallpox is still India and Pakistan, which in 1958 accounted for 218 000 cases out of the world total of 242 000, and in 1959 for 50 000 cases out of a total of 74 000. More than any other disease, smallpox is liable to be imported, especially by air, into countries normally free from it. This occurred several times during the past year.

In spite of increasing air traffic, yellow fever has not spread outside its usual foci in Africa and America. It exists principally as jungle yellow fever which affects monkeys and is rarely contracted by man. The annual incidence is now low, although an epidemic occurred at the end of 1959 in parts of Ethiopia and in the Blue Nile and Upper Nile Provinces of the Sudan, where at least 118 cases and 87 deaths from the disease were notified.

Contrary to general belief, typhus is not regressing in Africa, where Ethiopia is now the principal focus. In the Americas, the situation is constantly improving, and the number of cases dropped from 25 000 a year in 1946-50 to 7500 in 1956-60. There has also been a constant decline in the incidence of the disease in Asia since the end of the Second World War.

The introduction of modern insecticides has made it an easy matter to prevent relapsing fever, which is transmitted by lice and ticks. There have been 2 doubtful cases in the Americas and hardly any in Asia since 1957. Although the number of cases in Africa seems to be on the increase, the disease does not constitute a serious health problem there, except in Ethiopia.

WHO membership

Eight African States have recently become full Members of WHO by depositing with the Secretary-General of the United Nations formal instruments of acceptance of the WHO Constitution.

They are the Republic of Dahomey, the Central African Republic, the Republic of the Upper Volta, the Republic of the Niger, the Republic of Mali, the Republic of the Congo (Brazzaville), the Republic of the Ivory Coast, and the Republic of Senegal. This brings the number of States which are full Members of the Organization up to 98.

People and Places

Community water supplies in Ghana

WHO has sent a consultant team to Ghana to advise the Government on the development of a national programme for the improvement and extension of community water supplies.

Mr A. L. McClure, Deputy Chief Civil Engineer of the Crown Agents, London, England, will advise on the engineering aspects of the programme. Mr McClure served from 1926 to 1956 in the Malayan Public Works Service, where his last position was that of Deputy Director of Public Works. He has had wide experience in all types of civil engineering work, specializing in water supply engineering during the latter part of his service in Malaya.

Mr G. W. Putto, Lawyer and Vice-Director of the Dutch Government Institute for Water Supply at The Hague, will be concerned with the administrative and legal problems involved in setting up a national water supply agency and will advise the Government on measures to be taken in this connexion. Mr Putto has been active in water supply management for a number of years and was General Rapporteur on Legal Measures at the Brussels Congress of the International Water Supply Association in 1957.

Finally, the services of Dr H. T. Shenefield have been made available to the team for a limited period by the US International Co-operation Administration, where he is Chief of the Loan Administration Staff. Dr Shenefield will serve as financial adviser to the programme.

Leprosy control

Dr F. M. Noussitou, of Argentina, has been appointed by WHO to conduct a leprosy control project in Burma. A former President of the Argentine Society of Dermatology, Dr Noussitou has worked for WHO for several years, first in the ringworm control programme in Syria, then as team leader of the venereal disease control project in East Pakistan.

Venereal disease programme in Taiwan

Since 1953, the Government of Taiwan (China) has been establishing a comprehensive venereal disease control programme with help from WHO, UNICEF and bilateral agencies. The programme now covers the whole of Taiwan (with the Penghu Islands), and 431 health units, including Taiwan's 22 health centres, the associated health stations and several provincial, county and municipal hospitals, take part in it. The work has thus been integrated into that of the established health services from the start.

Dr Olav Idsøe, of Norway, has been appointed by WHO to undertake an evaluation of the programme and its achievements, and is at present visiting Taiwan for this purpose. Dr Idsøe has wide experience of venereal disease control in Europe, Africa, and the Eastern Mediterranean and Western Pacific Regions.

Prevalence of periodontal disease

Dr Jens Waerhaug, Professor of Periodontology and Crown and Bridge Prosthesis at the University of Oslo, Norway, has been appointed by WHO to undertake a pilot survey on the prevalence and distribution of periodontal disease among selected age groups in urban and rural communities in Ceylon.

A recognized authority on periodontal disease, Professor Waerhaug has done a considerable amount of research on the anatomy, histology and histopathology of the supporting structures of the teeth. In 1953-54 he spent a year in the USA as research associate at the University of Minnesota, and subsequently conducted courses

and gave lectures in his specialty to members of the dental profession in the USA, Australia, the United Kingdom, and Scandinavia. He acted as consultant to the WHO seminar on dental health, held in Adelaide, Australia, in February 1959, and to the WHO Expert Committee on Dental Health in August 1960.

Public health administration

At its twelfth session in 1961, the United Nations Committee on Information from Non-Self-Governing Territories will pay special attention to the question of social conditions in these territories. A study on health conditions, which is being prepared by WHO for the Committee's session, will deal with the organization of the health services in Kenya, particularly in rural areas.

Dr J. D. Kershaw, Medical Officer of Health for Colchester, England, has been appointed to undertake this study. His assignment includes a four-week visit to Kenya to study the health services there at first hand, followed by a period in Geneva to write his report. Dr Kershaw has undertaken several assignments for WHO, including the preparation of an earlier study—on long-term health planning—for the Committee on Information from Non-Self-Governing Territories.

Financing of medical care

As part of a WHO survey on the costs and financing of medical care, pilot studies were started in six countries in 1959. Mr B. Abel-Smith, Lecturer in the Department of Social administration of the London School of Economics, recently visited two of these countries—Sweden and Czechoslovakia—to assess the progress of the studies and to discuss with the authorities concerned the data so far collected. Mr Abel-Smith has already carried out a number of assignments for WHO in connexion with the survey. It is expected that most, if not all, of the pilot studies will be completed by the end of the year.

Tuberculosis in the Malagasy Republic

Dr Maurice Gilbert has been appointed by WHO to study the problem of tuberculosis in the Malagasy Republic, and to determine the extent to which the Organization can assist the Government in its efforts to control the disease.

Dr Gilbert, who was educated in Geneva and Paris, has been active in tuberculosis work for many years. He represents the International Union against Tuberculosis in its relations with WHO and with the International Labour Organisation.

Tuberculosis in cattle

"Bovine tuberculosis is probably not of great importance at present because in most parts of the world milk is routinely boiled before consumption, and in the other areas pasteurization of milk and control of bovine tuberculosis infection have been put into extensive practice. However, in countries where tuberculosis among cattle is a problem, it is also a menace to man, and in these countries complete control of tuberculosis cannot be achieved unless attention is also paid to the reduction, or preferably eradication, of tuberculosis in cattle. In some areas, studies to determine the possible role of tuberculosis in other animals as a source of infection for man are indicated."

From the seventh report of the WHO Expert Committee on Tuberculosis (*Wld Hlth Org. techn. Rep. Ser.*, 1960, 195)

Review of WHO Publications

TUBERCULOSIS

Bulletin of the World Health Organization, 1960, Volume 23, Number 4-5 (pages 421-694)

The progress made in recent years in the chemotherapy of tuberculosis has been such as to revolutionize the approach to the control of this disease. It is to a large extent because of the introduction of effective antituberculosis drugs, particularly isoniazid, that for the first time the possibility of eradicating tuberculosis can be envisaged. However, although in the last ten years extensive clinical trials have been made of different chemotherapeutic regimens, the problem of the best treatment of tuberculosis, in both medical and economic terms, is still far from being solved. This and other problems related to the chemotherapy of tuberculosis are the subject of the first six papers in this issue of the Bulletin.

In the first paper, W. McDermott reviews the present state of knowledge of the chemotherapy of pulmonary tuberculosis. The great advances that have resulted from the introduction of isoniazid are stressed: the most effective of the combined drug regimens in use today all include isoniazid, and it is this drug which provides the major part of their antituberculous action.

An important problem discussed in this paper is whether the large-scale use of isoniazid in home treatment programmes will result in a significant spread of isoniazid-resistant bacilli. Very little is as yet known about the risk to the community of the presence of persons excreting isoniazid-resistant organisms. McDermott suggests that the risk is considerably greater in areas with a low technological development and a high tuberculosis morbidity than in highly developed areas with a low tuberculosis morbidity. He concludes, however, that even in the former areas, the case for going ahead with the widespread use of isoniazid considerably outweighs the case for not going ahead. The risk to the community could be reduced by more selective treatment programmes, chemotherapy being combined with collapse or excisional therapy in certain patients.

The next five papers present the results of studies conducted by the Tuberculosis Chemotherapy Centre in Madras, South India. This centre was set up in 1956 under the joint auspices of the Indian Council of Medical Research, the Madras State Government, the World Health Organization and the Medical Research Council of Great Britain (MRC), to investigate problems of large-scale chemotherapy of tuberculosis under the conditions prevailing in a developing area.

In a previous study by the Tuberculosis Chemotherapy Centre,[1] it was shown that a year's domiciliary treatment with isoniazid plus PAS for all practical purposes gave as satisfactory results as a year's institutional treatment with the same combination of drugs. This finding suggested that domiciliary chemotherapy might be of considerable value in countries where the tuberculosis problem is aggravated by a shortage of hospital beds. Before domiciliary chemotherapy can be introduced on a larger scale, however, a number of important problems have to be evaluated. One of the most important is whether domiciliary treatment of " open " cases exposes their contacts to a special risk of infection. A study of this problem is described in the second paper in this issue. The results indicate that the place where the patients were treated—at home or in a sanatorium—did not influence the incidence of clinical tuberculosis or of tuberculous infection in their family contacts. Another problem concerns the risk of relapse after domiciliary chemotherapy as compared with institutional chemotherapy. The third paper reports on a twelve-month follow-up of patients who had attained bacteriological quiescence by the end of one year of combined chemotherapy either at home or in a sanatorium. This study included treatment either with isoniazid alone or with a placebo. It was found that the relapse rate of the " home " patients differed very little from that of the " sanatorium " patients

[1] See *Bull. Wld Hlth Org.*, 1959, 21, 51.

and, rather surprisingly, that continued treatment with isoniazid alone did not reduce the risk of relapse.

In recent years domiciliary chemotherapy with isoniazid alone has been used on an increasing scale in several developing countries. This regimen has many obvious practical advantages over the combined therapies but relatively little is known about its efficacy. A controlled comparison, which is reported in the fourth of the papers, indicates that treatment with isoniazid alone—in standard daily dosage (3.9-5.5 mg/kg body weight) or high daily dosage (7.8-9.6 mg/kg body weight)—is less satisfactory than the standard combined chemotherapy with isoniazid and PAS. The patients, who were all treated at home and mostly presented with cavitary disease, showed less improvement on isoniazid alone. In addition, a high frequency of peripheral neuritis was observed in the patients receiving a high dosage of isoniazid. The fifth paper gives a detailed report on the peripheral neuritis cases encountered in the controlled therapeutic comparison.

As described in previous reports, pretreatment cultures of tubercle bacilli from Indian patients included in the trials of the Tuberculosis Chemotherapy Centre have been found to have a higher average level of resistance to PAS than pretreatment cultures from British patients. An investigation, reported in the sixth paper in this issue, by the Centre and the MRC Group for Research on Drug Sensitivity in Tuberculosis reveals that the higher average resistance of the Indian strains is due to the presence of a small proportion of resistant organisms. There was, however, little, if any, evidence that the efficacy of the standard combination of isoniazid plus PAS was impaired in the Indian patients.

In recent years the isolation of atypical strains of mycobacteria from pulmonary and extrapulmonary lesions has been reported with increasing frequency. The reports refer mainly to Europe and the USA, and very little is yet known about the distribution of different mycobacteria in the developing countries. The next paper in this issue is concerned with a study carried out jointly by WHO, the Kenya Medical Department and the Tuberculosis Research Institute in Prague, on the isolation, typing and drug sensitivity of mycobacteria from the lymph nodes of African patients. All strains isolated proved to be of the human type, but in the case of some patients, previously untreated, the lymph node specimens showed granulation tissue typical of mycobacterial infection although no acid-fast bacilli were demonstrated either by culture or by guinea-pig tests. Thus the possible occurrence of atypical mycobacteria in African patients needs further investigation.

In the course of WHO/UNICEF-assisted tuberculosis surveys in Africa sputum specimens were sent to certain European laboratories for culture owing to the lack of adequate local laboratory facilities. Strikingly few positive cultures were obtained and those were usually only from specimens strongly positive on direct microscopy. The paper by L. Šula, T. K. Sundaresan & M. Langerová reports on an investigation into the influence of storage and transport—from Prague to Africa and back—on the survival of mycobacteria in pure cultures and in sputum specimens. There was a great decrease in the cultivability of the mycobacteria contained in the material, which was treated in the same way as the routine specimens received from the African tuberculosis surveys.

A second condition for the successful culturing of mycobacteria is the sensitivity of the diagnostic medium. The Löwenstein-Jensen (L-J) medium commonly used gives good results when properly made but its sensitivity varies greatly when it is prepared in different laboratories, thus precluding international comparison of results. As reported in the next paper, comparative trials carried out at the Tuberculosis Research Institute in Prague with L-J medium from seven national laboratories have demonstrated that even media prepared in different departments of the same institute are of unequal sensitivity for both laboratory strains and primary cultures. These results stress the need for a standard diagnostic medium. It is suggested that a freeze-dried medium which would keep for long periods would serve this purpose; it could be prepared and tested for sensitivity in one laboratory and then distributed for general use.

The paper by O. Horwitz & J. Knudsen of the Danish Tuberculosis Index reports on a four-year follow-up of the attenders and the non-attenders at the Danish mass campaign in 1950-52 which combined case-finding and BCG vaccination. The incidence of tuberculosis was found to be

lower among the attenders. From a detailed comparison of the two groups the authors conclude that the lower morbidity rate among the attenders reflects the effect of the mass campaign, since in the campaign cases were detected early that would otherwise have remained undiagnosed until subsequent years.

Observations of particular relevance to the standardization of tuberculin are reported in the paper by G. W. Comstock. In a comparison of two purified tuberculins—PPD-S and RT 19-20-21—in schoolchildren in the south-eastern part of the USA, a marked qualitative difference was found between them. In children with low-grade sensitivity, presumably of non-specific origin, the reactions to RT 19-20-21 tended to be larger than those to PPD-S. In children with high levels of sensitivity the reactions to PPD-S tended to be larger. Similar findings have been reported previously [2] from other countries (Nigeria and Mauritius) where low-grade, presumably non-specific, sensitivity is widespread.

Simultaneous duplicate tuberculin testing is often used in experimental work. A possible source of error in this method is brought to light by the data reported in the last paper in this issue. In a study in BCG-vaccinated infants given either a single test with 10 TU of old tuberculin or a duplicate test with 10 TU in one arm and 100 TU in the other, it was found that the reactions to the low-dose test were reduced in size when this test was given simultaneously with a high-dose test.

[2] See *Bull. Wld Hlth Org.*, 1958, **19**, 845.

Expert Committee on Poliomyelitis : Third Report (*World Health Organization Technical Report Series*, No. 203), Geneva, 1960, 53 pages. Price: 3/6, $0.60, or Sw.fr. 2.—. Published also in French and Spanish.

This report is discussed at length in the article on page 462.

Study Group on Chagas' Disease : Report (*World Health Organization Technical Report Series*, No. 202), Geneva, 1960, 21 pages. Price: 1/9, $0.30, or Sw.fr. 1.—. Published also in French and Spanish.

This report is discussed at length in the article on page 469.

INDEX

ABBAS, M., 256
ABBES, Y. BEN, 256
ABEL-SMITH, B., 483
ADAN, B., 54
Addiction-producing drugs, 50, 159
Aëdes aegypti eradication, Brazil, 225-226
Africa, goitre, 343-344
  leprosy, 10, 18, 21, 34
  malaria, 79
  mental health, 73-74
  public health, 394-399
  Regional Committee, 45-46, 440-441
  smallpox, 82
  urbanization, 173-179
AFRIDI, M. K., 256
Air pollution, 105, 426-431, 468
Aircraft disinsection, 448-449
ALAKIJA, O. B., 440
ALDRIDGE, PHYLLIS D., 334
ALEXANDER, A. D., 237
ALVING, A. F., 239
Americas, goitre, 339-340
  Guatemala City Zone Office, 114-116
  nursing, 208
  poliomyelitis, 226-228
  Regional Committee, 46-48, 441-443
  zoonoses, 321-327
  See also Latin America
Anaemia, Mauritius, 477-478
Anaesthesiology course, 162
ANDERSON, M. M., 207
ANDREWES, C. H., 413
Annual Epidemiological and Vital Statistics 1956, 243
Annual Epidemiological and Vital Statistics 1957, 376
Anophelines, feeding preferences, 400-403
  insecticide resistance, 123-124
ANSARI, N., 164
ANTAL, G. M., 290
Antibiotics, 411-412
ANTONA, D. D', 81
ANTUNES, P., 126
ANWAR, S., 443
Architecture and psychiatric services, 87-89
ARUNAVEJA, SAKORN, 373
Asia, goitre, 341-343
  leprosy, 10, 35
Atomic energy, medical aspects, 161-162, 304-305, 379-384
AUJALEU, E. J. Y., 151, 272, 275, 444
Australia, goitre, 344-345
Automation, mental health problems, 41-43
Auxiliary personnel, training, 449
Aviation, hygiene and sanitation, 219-222, 448-449

BAENA, J. M., 256
BALTAZARD, M., 419
BANKS, A. L., 53
BARANSKI, R., 256
Basutoland, endemic goitre, 207
BAZIN, H., 108
BCG vaccination, leprosy, 3, 17
  tuberculosis, 133, 152
BCG vaccine, production, 81
BEAVER, P. C., 414
Belgian Congo, poliomyelitis vaccination, 139-140
BENTZON, W., 205
Bibliography on Bilharziasis 1949-1958, 243
BIERDRAGER, J., 164
Bilharziasis, 62, 121-122, 303
  bibliography, 243
Biological material, postage, 473-474
Biological standardization, 158-159
Biological substances, requirements, 78
Black-flies, 189-190
BLANKHART, D. M., 163
BLIOUMEL, NINA, 241
Bornholm disease, Upper Silesia, 207
BOUSSINGAULT, J. B., 361
BRAND, P., 414
BRAVO, A. L., 164, 373
Brazil, *Aëdes aegypti* eradication, 225-226
BRIDGMAN, R. F., 413
BROWN, A. W. A., 333
BRUCE-CHWATT, L. J., 373
Brucella, classification, 434-435
Brucellosis, vaccination, 135
BTESH, S., 373
BURMA, leprosy, 33
BURTON, J., 61
BUSTAMANTE, M. E., 256

CALSEYDE, P. J. J. VAN DE, 444
Cambodia, smallpox, 240
CAMBOURNAC, F. J. C., 45, 394, 440
Cancer, lung, 201-203
  statistics, 116-120
CANDAU, M. G., 213, 218, 257, 264, 272, 275, 379, 387, 431
Cardiology, scholarship, 367
Cardiovascular diseases, mortality, 228-231
  See also under name of disease
CARPENTER, C. M., 238
CARSTAIRS, G. M., 86
CASTILLO, D., 151

Ceylon, venereal infections and treponematoses, 57-59
Chagas' disease, 287-288, 469-471
CHAMBERLAYNE, E. C., 321
CHARLES, SIR JOHN, 255
CH'EN, CHENG-TEH, 85
Child guidance, 413
Child Guidance Centres, 373
Children, dental health, 288-289
Chile, water fluoridation, 160-161
CHIPMAN, S. S., 372
Cholera, 75-76, 198, 199
Cirrhosis of the liver, France, 471-472
CLEMENTS, F. W., 345, 353, 356
Clonorchiasis, Korea, 161
Colombia, poliomyelitis vaccination, 140-141
Communicable diseases, 292-293, 481
  in schools, 43-45
  notification, 71
  vaccination, 131-136, 311-314, 329
Comparative Pharmacology of Some Psychotropic Drugs, 376
Congo, Republic of (Léopoldville), public health services, 438
Cor pulmonale, 481
COSTA, A., 320
Cretinism and goitre, 353-355
CROFT, C. C., 242
CROSSKEY, R. W., 190
CRUICKSHANK, R., 209
Czechoslovakia, poliomyelitis vaccination, 144

D'COSTA, J. F., 290
DDS, in leprosy control, 11, 17, 18
Death, causes, 194-196
Dental health, 160-161, 288-289, 411
DE SMET, M. P., 345, 356
Diarrhoeal diseases, 89-91, 179-184, 330, 436-438
DÍAZ LIRA, G., 287
Differential Diagnosis of Yaws, 375
Director-General of WHO, annual report, 213-218, 257, 297
Disarmament and funds for health, 152-153, 262
DOBBS, R. H., 241
DORION, MARCÈLE, 163
DOROLLE, P., 45, 445
Drinking-water, international standards, 220
  scientists engaged in research on, 207-208
DUBUISSON, J., 272, 274
DUTOIT, J., 272

EARLE, K. V., 451
Eastern Mediterranean Region, malaria, 82
  nursing education, 63-66
  Regional Committee, 476-477
EDDEY, L. G., 289
Education and training, 217, 305-306, 412
Education and training (*continued*)
  anaesthesiology, 162
  auxiliary personnel, 449
  basic medical sciences, 412
  environmental sanitation, 51-52, 162, 480
  health education, 52, 232-233
  health statistics, 480-481
  malaria staff, 149-150
  nurses, 51, 63-66, 366-367, 371
  nutrition, 124, 332
  psychiatry, 331
  public health, 379-384, 410-411
  radiation medicine, 379-384, 478
ELIOT, MARTHA, 372
Endemic goitre, *see* Goitre
Environmental sanitation, training of personnel, 51-52, 162
Epidemiological and statistical information, 75-78, 154-156, 194-200, 226-231, 321-327, 407-408
Epidemiological Methods in the Study of Mental Disorders, 126-127
Epidemiology, cancer, 201-203
  in health administration, 479
  mental disorders, 126-127, 156-157
  serological, 40-41, 184-189
ETEMADIAN, N., 151
Europe, dental health, 288-289
  food-borne diseases, 368
  goitre, 340-341
  leprosy, 10
  malaria, 193, 240
  mental hospitals, 108
  nursing administration, 81-82, 371
  Regional Committee, 444-445
  sanitary engineers, 480
  vaccination, 52, 131-136
EVANG, K., 125, 268
Executive Board, membership, 261
  twenty-fifth session, 151-153
Eye diseases, 51, 145-146, 304

FANG, I. C., 446, 447
FARAH, A. R., 476
FARINAUD, M. E., 85
Fellowships, 412
  appraisal, 157-158
  leprosy, 13
FENDALL, N. R. E., 289
Filariasis, 300-301
FINCH, C. A., 53
FITZJOHN, R. A., 414
Fluoridation of water, Chile, 160-161
Food additives, 124
Food-borne diseases, 78-79
  Europe, 368
FRAISSE, J., 83
France, cirrhosis of the liver, 471-472

FRANDSEN, J., 444
FREDERIC IX, King of Denmark, 444
French Equatorial Africa, leprosy, 24
French West Africa, leprosy, 24

GARNHAM, P. C. C., 333
GAUTHIER, M., 83
GAY PRIETO, J., 3
GEAR, H. S., 52
GENDEREN, H. VAN, 53
Ghana, leprosy, 24
  yaws, 222-224
GIBIŃSKI, K., 207
GILBERT, M., 483
GILROY, A., 85
GODDARD, H. A., 371
Goitre, 337-365
  Basutoland, 207
  control, 356-361
  cretinism, 353-355
  distribution, 339-345
  facts and theories, 345-353
  iodized salt, 361-365, 474-475
  Italy, 320-321
GÓNGORA, J., 337
Gonococcus cultures, transport, 204-205
Gonococcus strains, resistance to penicillin, 123, 238-239
Gonorrhoea, 204-205
GRASSIOULET, J., 290
GRUNDY, F., 452
Guide to Hygiene and Sanitation in Aviation, 220, 243

HACKETT, C. J., 144
HAIRSTON, N. G., 415
Haiti, yaws, 80-81
HAM, H. J., 125
HARINGTON, C. R., 345
HARRIS, R., 162
Health education, 59, 79-80
  films, 287
  teacher preparation, 52, 232-233
Health legislation, communicable diseases in schools, 43-45
  goitre, iodine prophylaxis, 474-475
  pharmaceutical preparations, 285
Health statistics, 243, 480-481
  cancer, 116-120
  hospital statistics, 69-71
  international work in, 66-73, 116-120, 146-148, 191-193
Health survey, Seychelles, 109-111
Heart disease, pulmonary, 481
HERLITZ, G., 390
HOLMAN, J. C. M., 337, 361
HOLTEN, I. VON., 163
HORSTMANN, DOROTHY, 142
HORWITZ, A., 47, 321, 410, 441
HOSKINS, W. M., 413
Hospital statistics, 69-71
Hospitals, mental, 87-89, 108
HOUSSA, P., 242
HUDDLESON, I. F., 435
HUTCHISON, A., 333
HYDE, H. VAN ZILE, 441
Hypertension, pathogenesis, 332

IDSØE, O., 482
Immunology, 184-189
India, immunization programme, 447-448
  tuberculosis control, 280-281
Indonesia, leprosy, 33
Industry, psycho-social environment in, 276-279
Infant mortality, 407-408
Influenza, diagnosis, 122-123
  1957-58 pandemic, 83
  vaccination, 134
Insect-borne diseases, 370-371
Insecticide resistance, 204
  in anophelines, 123-124
International Commission on Radiological Protection, 106-107
International Commission on Radiological Units and Measurements, 108
International non-proprietary names for pharmaceutical preparations, 50, 244-251
International Reference Centre for Respiratory Viruses, 413
International Sanitary Regulations, 219, 306
Iodine and goitre, 357-361
Iodized salt in prophylaxis and treatment of goitre, 361-365, 474-475
Isoniazid in prophylaxis of tuberculosis, 286-287
Italy, goitre, 320-321

JOHN XXIII, His Holiness Pope, 431
JUCHNIEWICZ, M., 444

KAUFMANN, P. C., 290
KAUL, P. M., 259
KELLY, F. C., 339, 345, 353, 356
KERSHAW, J. D., 483
KHRUSHCHEV, N., 256
KIMBALL, O. P., 337
KOMIYA, Y., 241
Korea, clonorchiasis, 161
  paragonimiasis, 161
KORNER, B., 205
KPROTSRA, G. V., 440
KRAMER, M., 86
KRANENDONK, O. J. M.., 446
KRECH, U., 333

La fin des asiles, 108
LAIRD, S. M., 57
LANGER, P., 345
Larvicides, spreading agents in, 82-83
Latin America, leprosy, 10
  leptospirosis, 237-238
  public health teaching, 410-411
  water supplies, 112-114
LATTUF, L., 441
League of Arab States, relations with WHO, 262
LECHAT, M., 210
LEE, R. C. K., 445
LEMIERRE, A. T., 414
Leprosy, 3-39, 159-160, 302
  BCG vaccination, 3
  classification, 5
  control, 11
  differential diagnosis, 25-32
  distribution, 8-11
  economic aspect, 35-36, 39
  history, 19-20
  international projects, 22-24, 33-34
  rehabilitation, 39
  role of WHO, 11-15
  treatment, 37-38
Leptospirosis, Americas, 237-238
LEROUX, O., 371
Levels of living, 146-148
LINDEMANN, E., 86
LISSITZKY, S., 345
LÖFSTRÖM, G., 53
LØNBORG-MADSEN, I., 289
LOWENSTEIN, F. W., 356
LUBE, C., 287
Lung cancer, 201-203

MACCALLUM, F. O., 242
MCCARTNEY, W., 361
MCCLURE, A. L., 482
MACDONALD, G., 85
MACKENZIE, M., 209
MACHADO VENTURA, J. R., 441
MAFFI, M., 85
MAGNUSSEN, ELI, 53
Malaria, 79-80, 151-152, 231, 259-260, 264-267, 291-292, 279-298, 370, 400-403, 431
  Africa, 79
  chemotherapy, 239-240
  Eastern Mediterranean Region, 82
  epidemiology, 432-434
  Europe, 193, 240
  training of staff, 149-150
Malaria Eradication Special Account, 260, 289, 431
MANI, C., 231, 443
MANTILLA, L. F., 242
Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, 194
MARINE, D., 356
MARINESCU, V., 444
MARKELIUS, S. G., 272, 275
MARTIN, M. P. D., 334
MARTÍNEZ-DOMÍNGUEZ, V., 3
MARTINS, J. P., 446
MASUREL, N., 83
MATOVINOVIĆ, J., 290, 356
Mauritius, anaemia, 477-478
MAXWELL, J. P., 290
MAXWELL-LYONS, F., 145
Medical literature, international exchange, 267
Medical research, 52
  role of WHO, 151, 261, 387-390
Medical sciences, teaching, 412
Mediterranean area, water supplies, 384-387
MEILLON, B. S. J. DE, 86
Mental disorders, epidemiology 126-127, 156-157
Mental health, 91-93, 293, 479-480
  Africa, 73-74
  and automation, 41-43
  in industry, 276-279
Mental hospitals, 87-89, 108
METCALFE, A. J., 151
Mexico, rural health, 409-410
Microbial sensitivity tests, standardization, 411-412
MILCU, S., 345
Milk, dry skim, distribution by UNICEF, 390-393
  hygiene, 282-284
MITCHISON, D. A., 53
MOLITOR, L., 444
Molluscicides in bilharziasis control, 121-122
MONTALVO, A., 287
Morbidity statistics, 66-73
Morocco, trachoma, 145-146
Mortality, cardiovascular diseases, 228-231
  infant, 407-408
MORTARA, M., 320
MSANGI, A. S., 82
MULDER, J., 83
MUÑOZ, J. A., 207, 337, 356
MURPHY, G., 162
MURRAY, J., 286

NABILSI, A., 476
Narcotic drugs, international control, 309-311
Natural foci of infection, 370-371
New Zealand, goitre, 344-345
Nigeria, leprosy, 23-24
NOUSSITOU, F. M., 482
Nursing, Americas, 208
Nursing administration, Europe, 81-82, 371
Nursing education, 51, 366-367, 371
  Eastern Mediterranean Region, 63-66

Nutrition, 390-393
education and training, 124, 332
NYSWANDER, DOROTHY, 126

Occupational health, 276-279
Onchocerciasis, 189-190
OPPENOORTH, F. J., 451
ORBELL, E., 372
ORDWAY, N., 176, 177
OUGHTON, J. G., 85
PAGIRAS, E. D., 372
PALMER, M. F., 163
PALTHEY, G., 256
PAMPANA, E. J., 86
Paragonimiasis, Korea, 161
Paraguay, leprosy, 34
PARKER, A., 430, 431
PARKER, W. S., 126
PATTERSON, HELEN A., 454
PATWARY, K. M., 86
PAUL, J. R., 185, 189
PAYNE, A. M.-M., 164, 184
PAYNE, F. J., 163, 241, 330
Penicillin, reactions to, 160
resistance of gonococcus, 123, 238-239
PENIDO, M. M., 151
PENMAN, D., 451
PEREIRA, E. D. C., 57
PÉREZ, C., 356
Periodicals, indexing and abstracting, 48
Periodontal disease, 411
Peru, water supplies, 288
Pesticides, 48-49
PETERSON, J. S., 241
Pharmaceutical preparations, classification, 285
international non-proprietary names, 50, 244-251
specifications, 81
Philippines, leprosy, 33-34
PHILLIPS, P. M. J., 440
PIERRE-NOEL, L., 371
Plague, 75, 154
epidemiology, 419-426
PLATTER, F., 353
Poland, Bornholm disease, 207
poliomyelitis vaccination, 144
Poliomyelitis, 303-304, 331
Americas, 226-228
vaccination, 49, 133, 138-141, 142-144, 462-468
vaccines, 137-142, 330-331, 462-468
PONCE DE LEÓN, J., 287
PONTI, G., 272
Precipitin test, 400-403
Primaquine, sensitivity to, 239-240
PROTHERO, R. M., 163
Psychiatric hospitals, *see* Mental hospitals
Psychiatric Services and Architecture, 87-89
Psychiatry, psychotropic drugs in, 205-206
social, 276-279
teaching, 331
Psycho-social environment in industry, 276-279
Psychotropic drugs in psychiatry, 205-206
Public health, Africa, 394-399
international co-operation, 152-153, 268-269
Latin America, 410-411
teaching, 379-384
Public health administration, epidemiology in, 479
study tours, 331-332
Public health services, 262, 305, 449
Congo, Republic of (Léopoldville), 438
local, 51, 233-236
USSR, 97-105
Publications of WHO, review, 87-89, 126-127, 243, 291-293, 373-376, 484-486
PUFFER, R. R., 321
Pulmonary heart disease, 481
PUTTO, G. W., 482

Quarantine, international, 75-78, 306-309

Rabies, 81, 439, 455-461
Radiation, 304-305
effect on human heredity, 121
medical supervision, 50
protection, 106-108, 152, 208-209, 260-261
Radiation medicine, training and teaching, 379-384, 478
RAFI, S. M., 86
RAMALINGASWAMI, V., 337, 356
RASKA, R., 189
RATNER, V. M., 60
Rehabilitation, medical, 450, 479
leprosy, 39
REINHARDS, J., 145
Relapsing fever, 78
RENOUX, G., 435
Reports of expert groups, 40-43, 78-79, 121, 156-160, 201-203, 232-236, 282-284, 327-329, 366-367, 403-406, 439
Research, medical, *see* Medical research
Respiratory viruses, 413
REVELL, V., and Co., 272, 274
Review of WHO publications, *see* Publications of WHO, review
REYN, ALICE, 205
Rickettsial diseases, diagnosis, 449-450
RIEDMATTEN, Rev. Father H. DE, 431
ROBERTSON, SIR HOWARD, 272, 275
ROCHE, J., 345
Rural health, Mexico, 409-410

SAARINEN, E., 272, 274
SABIN, A., 137

SACQUET, E., 435
SANDISON, R. A., 205
SANDOSHAM, A. A., 451
Sanitary engineers, 480
Sanitary inspectors, training, 162
SATSARA, VANA, 373
SAUTER, A., 444
SCOTT, D., 222
SCRIMSHAW, N. S., 356
SEBSEBIE, M., 476
SEELIGER, H. P. R., 368
SENOV, P., 242
Serological epidemiology, 40-41, 184-189
Seychelles, health and morbidity, 109-111
SEYFFER, CHARLOTTE, 63
SHAMMAS, M. A., 125
SHENEFIELD, H. T., 482
SHOIB, M. O., 164
SIEGEL, B. B., 157
SIEGEL, M. P., 47
SILVEIRA, J., 372
Simulium, 189-190
Smallpox, 76-77, 198, 199, 260, 301-302, 314-317
  Africa, 82
  Cambodia, 240
SMORODINTSEV, A., 290
SNEDDEN, W. W., 339, 345, 353, 356
SOPER, F. L., 48
South-East Asia, leprosy, 35
  Regional Committee, 443-444
SOUZA, A. DE, 126
SPARROW-GERMA, HÉLÈNE, 84
SPECTER, G., 210
SPITZ, A. J. W., 109
STANBURY, J. B., 345
STANDFAST, A. F. B., 206
STOTT, G., 477
STOTT, H., 451
Suicide, 196-198
Sulfones in leprosy control, 11, 20
SUVARNAKICH, K., 443
SYMAN, S., 476

TABA, A. H., 476
TAYLOR, J., 436
TAYLOR-ROBINSON, D., 413
TCHOUNGI, S. P., 45, 440
TEN YOON FONG, 445
Thailand, leprosy, 33
  yaws, 318-319
TORRICO, R. A., 333
TORROELLA, J., 85
Trachoma, 51
  antibiotic treatment, 145-146
TRUHAUT, R., 53
TSAI, FANG-CHIN, 126
TSCHUMI, J., 272, 273, 274
Tuberculosis, 298-300, 332, 403-406, 479, 484-486
  bovine, 483
  chemotherapy, 286-287
  home and sanatorium treatment, 280-281
  vaccination, 133, 152
TURBOTT, H. B., 256, 257, 263, 271
TURNER, L. H., 84
Typhoid fever, vaccination, 134-135
Typhoid vaccine, 206
Typhus, 77, 288
TYRRELL, D. A. J., 413

Uganda, leprosy, 24, 33
UNICEF *see* United Nations Children's Fund
Union of Soviet Socialist Republics, goitre, 341-343
  maternal and child health, 100
  occupational health, 100, 102
  poliomyelitis vaccination, 138-139, 142-144
  public health services, 97-105
United Nations Children's Fund, 14-15, 153, 390-393
Urbanization, Africa, 173-179
USSR, *see* Union of Soviet Socialist Republics

Vaccination, 131-136, 311-314, 329, 369-370
  brucellosis, 135
  diphtheria, 135
  Europe, 52, 131-136
  India, 447-448
  influenza, 134
  paratyphoid fever, 134-135
  pertussis, 135
  poliomyelitis, 49, 133, 138-141, 142-144, 462-468
  tetanus, 135
  tuberculosis, 133, 152
  typhoid fever, 134-135
Vaccination certificates, 124-125
Vaccine, BCG, 81
  poliomyelitis, 137-142, 330-331, 462-468
  typhoid, 206
VACHROTAI, S., 290
VAGO, P., 272, 275
Vatican, contribution to Malaria Eradication Special Account, 431
Vector control, 204
  at airports, 221-222
VEGA-RIVERA, R., 409
VELASCO-ALZAGA, J., 452
Venereal infections and treponematoses, 303, 327-329
  Ceylon, 57-59
  See also under name of disease
VERGARA, A., 390
VERHOESTRAETE, L., 452
VIERNE, A. 275
VIG, G., 372
Virus diseases, diagnosis, 449-450

Viruses, arthropod-borne, 450
respiratory, 413
VISWANATHAN, D. K., 240
Vital statistics *see* Health statistics
VRIES, J. DE, 290

WADSWORTH, G. R., 125
WAERHAUG, J., 482
WALKER, A. J., 45
WALLGREN, A., 390
WARMANN, J. ST G., 45
Water fluoridation, Chile, 160-161
Water supplies, Latin America, 112-114
and goitre, 349-350
Mediterranean area, 384-387
Peru, 288
See also under Drinking-water
WEBER, A., 145
WEEKS, E. B., 373
WEITZ, B., 401
Western Pacific Region, course on health statistics, 480-481
leprosy, 35
Regional Committee, 445-447
WHO Library News, 48
WILLIAMS, J. E., 210
WILLIAMS, N., 45
WILSON, DAGMAR, 337
WINGREN, J. E., 210
WINSLOW, C.-E. A., 268
WITT, V. M., 333
WOLMAN, A., 112
Work of WHO, The, 1959, 213
World Health Assembly, Fourteenth, place, 153, 263
World Health Assembly, Thirteenth 255-263, 297-306
President, 263
technical discussions, 263
World Health Day 1960, 209
World Health Organization, budget for 1961, 151, 259
financial resources, 153, 262, 268-272
flag, 153
Headquarters, accommodation, 153, 261, 272-275
structure, 241
members, admission, 257, 258, 481-482
programme for 1961, 151
publications, 262, *see also* Publications of WHO, review
World Health Year, 153, 262

YATES, G., 309
Yaws, 144, 215
Ghana, 222-224
Haiti, 80-81
Thailand, 318-319
YEKUTIEL, P., 432
Yellow fever, 76, 155-156, 225-226

ZAKI, A. A., 476
ZHDANOV, V. M., 311
Zoonoses, Americas, 321-327

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